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TOXOPLASMIC ENCEPHALOMYELITIS

VII. SIGNIFICANCE OF OCULAR LESIONS IN THE DIAGNOSIS OF INFANTILE OR CONGENITAL TOXOPLASMOSIS

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Human toxoplasmosis, a protozoan infection, was first encountered in infants as a severe disseminated encephalomyelitis,[1] after which it was observed in older children as a milder form of encephalitis[2] and in adults as a generalized infection with pulmonary involvement.[3] The large reservoir of spontaneous toxoplasmic infection in rodents and in birds is the most likely source of the human infection; however, no

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1. Wolf, A.; Cowen, D., and Paige, B. H.: (*a*) Human Toxoplasmosis: Occurrence in Infants as an Encephalomyelitis; Verification by Transmission to Animals, Science **89**:226-227 (March 10) 1939; (*b*) Toxoplasmic Encephalomyelitis: III. A New Case of Granulomatous Encephalomyelitis Due to a Protozoon, Am. J. Path. **15**:657-694 (Nov.) 1939; (*c*) Toxoplasmic Encephalomyelitis: IV. Experimental Transmission of the Infection to Animals from a Human Infant, J. Exper. Med. **71**:187-214 (Feb.) 1940.

2. Sabin, A. B.: Toxoplasmic Encephalitis in Children, J. A. M. A. **116**:801-807 (March 1) 1941.

3. Pinkerton, H., and Weinman, D.: Toxoplasma Infection in Man, Arch. Path. **30**:374-392 (July) 1940. Pinkerton, H., and Henderson, R. G.: Adult Toxoplasmosis: A Previously Unrecognized Disease Entity Simulating the Typhus-Spotted Fever Group, J. A. M. A. **116**:807-814 (March 1) 1941.

definite evidence of the mode of transmission from the lower animals to man is available.

The prominence and the regular occurrence of lesions in the eyes were stressed in previous papers of this series and in related publications in which the infantile form of the disease was first described.[4] These lesions, together with the symptoms and signs of widespread involvement of the central nervous system, frequently including internal hydrocephalus, convulsions which appeared at birth or soon thereafter and cerebral calcification detected by roentgenographic methods, comprised the outstanding features of the new syndrome. The data acquired in a retrospective study of the clinical facts in the primary series of cases of toxoplasmic encephalomyelitis, identified at necropsy by the characteristic pathologic picture [5] and by the isolation in some of the cases of the causative protozoon,[6] led to the recognition of the first 6 clinical cases of the disease. The nature of the condition was confirmed by the identification of neutralizing antibodies to Toxoplasma in the serum in all these cases. A detailed description of the clinical and laboratory data in these cases was recorded by three of us in the preceding publication of this series.[4c] It is the purpose of this report to present as a unit the ocular findings in infantile toxoplasmic encephalomyelitis, to compare and arrange them in a sequence which may clarify their development and to point out in what way they may be unique and diagnostic. The accompanying drawings of the eyes of 3 of the patients depict in detail the ophthalmoscopic range of variation of the intraocular lesions. The clinical findings in the pertinent cases are summarized only briefly, since detailed accounts of these already have been published.[4]

REPORT OF CASES

CASE 1 (Cowen, Wolf and Paige [4c]).—P. D., a girl aged 3 years and 9 months, had generalized convulsions, poor vision and left internal strabismus since early infancy and showed mental retardation and defective speech. There was roentgenographic evidence of small areas of intracerebral calcification at the age

4. (*a*) Wolf, A., and Cowen, D.: Granulomatous Encephalomyelitis Due to an Encephalitozoon (Encephalitozoic Encephalomyelitis), Bull. Neurol. Inst. New York **6**:306-371 (July) 1937. (*b*) Paige, B. H.; Cowen, D., and Wolf, A.: Toxoplasmic Encephalomyelitis: V. Further Observations of Infantile Toxoplasmosis; Intra-Uterine Inception of the Disease; Visceral Manifestations, Am. J. Dis. Child. **63**:474-514 (March) 1942. (*c*) Cowen, D.; Wolf, A., and Paige, B. H.: Toxoplasmic Encephalomyelitis: VI. Clinical Diagnosis of Infantile or Congenital Toxoplasmosis; Survival Beyond Infancy, Arch. Neurol. & Psychiat. **48**:689-739 (Nov.) 1942. (*d*) Wolf, Cowen and Paige.[1b]

5. Wolf, Cowen and Paige.[1b] Wolf and Cowen.[4a] Paige, Cowen and Wolf.[4b]

6. Wolf, Cowen and Paige (footnote 1 *a* and *c*). Paige, Cowen and Wolf.[4b]

of 3 years. Pronounced internal hydrocephalus was demonstrated by ventriculography at the age of 3 years and 6 months, at which time old, healed chorioretinitis was observed bilaterally.

Ophthalmologic Examination.—The level of visual acuity could not be determined with accuracy because of the lack of cooperation; however, although central vision appeared to be lacking, relatively small objects, such as a pen flashlight, were recognized when carried through the areas of peripheral vision of either eye, and light projection was normal in all quadrants. The action of the lids and the ocular motility of each eye appeared to be normal, and there was bilateral searching nystagmus. There were alternating esotropia of 40 degrees and right hypertropia of 4 degrees. The left eye usually dominated on fixation, and convergence ability was not demonstrable. The anterior segment of each eye

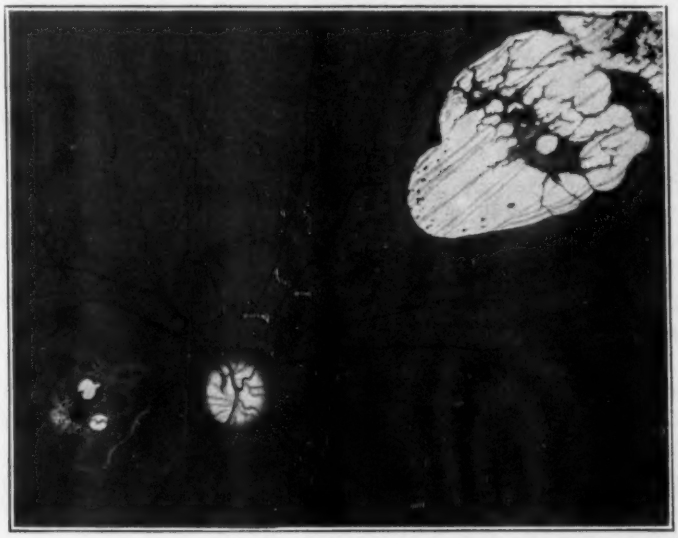

Fig. 1 (case 1).—The right eye. The first six figures, showing toxoplasmic chorioretinitis, were drawn by Mr. E. G. Bethke, Institute of Ophthalmology, Presbyterian Hospital, New York.

was essentially normal, but the pupils when tested with light directly and consensually exhibited moderate sluggishness of reaction, while the right consistently was minimally larger than the left.

Ophthalmoscopically, the right eye exhibited primary optic nerve atrophy of advanced degree, and the retinal vessels were moderately narrowed in caliber throughout. Two large areas of old, healed chorioretinitis were observed. The smaller of these occupied the macular area and measured approximately 1½ disk diameters in diameter. It was fairly well demarcated, was irregularly round and was depressed slightly below the level of the adjacent uninvolved portion of the retina. There was brownish black granular extensive and irregularly diffuse pigment deposition within this lesion, into which there extended a few retinal

vascular twigs. Two small round rather punctate areas of chorioretinal atrophy, centrally placed in this area, permitted visualization of the sclera. The inferonasal margin of the lesion was thickened as a result of low grade glial tissue proliferation, and just peripheral to the margin there was finely granular retinal pigmentation. No edema or other evidence of inflammatory activity was observed (fig. 1).

The larger lesion was oval in shape and rather sharply marginated by granular black pigment. It was situated in the upper nasal quadrant with its long axis at about 45 degrees to the horizontal. It was 4 disk diameters wide, and, although its peripheral limits could not be determined ophthalmoscopically, its near, or central, border was 5 disk diameters from the upper nasal margin of the optic papilla. The entire area exhibited almost complete chorioretinal atrophy, and the yellowish white glistening sclera was highly visible throughout, except for irregular coalescent black granular pigment deposits arranged in a pseudostellate pattern over the base of the lesion, which was marginated by somewhat similar pigmentation. A number of rather straight attenuated deep choroidal arteries traversed the base of this lesion in a radial manner throughout its length. Ophthalmoscopically, healing appeared long since to have been complete. The retina and choroid, except for the areas described, exhibited no other visible abnormalities. The media were clear.

Primary optic nerve atrophy of advanced degree was also present in the left eye, but ophthalmoscopically it was somewhat less marked than that observed in the right eye. The retinal vessels were smoothly and moderately attenuated in caliber. Temporally, the midsector of the disk was partially obscured by a moderately vascularized round slightly elevated (1 D.) glial mass with a light reddish brown finely granular pigmented surface. This mass also obscured a small area of the juxtapapillary portion of the retina and was one third the size of the disk. It appeared to have its origin in the retina immediately temporal to the disk proper. A few fine linear bands of faint gray scar tissue emanated from the depth of this area temporally and so traversed the anterior layers of the retina to connect with the nasal margin of a large central old, healed chorioretinal lesion. This lesion was triangular in shape, with the apex directed toward the disk and the base toward the temple. It was approximately 6 disk diameters in length, and its grossly scalloped margins were pigmented irregularly and presented some segments that were sharply defined; however, marginal definition was obscured by the diffuse, extensive, fine to coarse gray-black choroidal pigment. This pigment extended inward into the lesion and downward in pseudopodic fashion, and some of the extensions had joined with denser but paler areas of pigment deposition that emanated from, and bordered on, a gray, homogeneous, moderately elevated (3 D.) gourd-shaped mass of glial proliferation centrally situated within the main lesion. The yellowish white sclera was extensively visible because of the widespread chorioretinal atrophy within the lesion. A number of choroidal arteries that overlay the sclera traversed the base of the main lesion. These varied in caliber, but all appeared to have become attenuated to some extent, since most of them traveled a relatively straight course. The retina and choroid were otherwise normal ophthalmoscopically, and the media were clear (fig. 2).

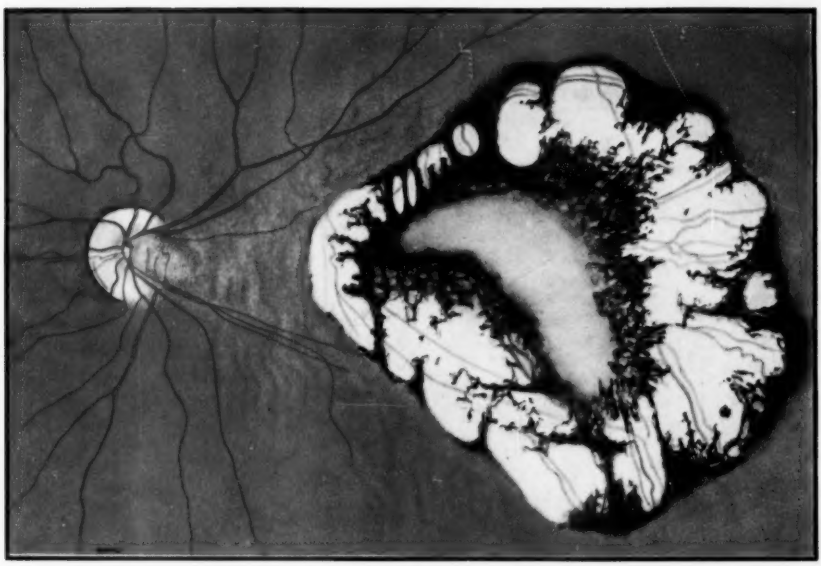

Fig. 2 (case 1).—The left eye.

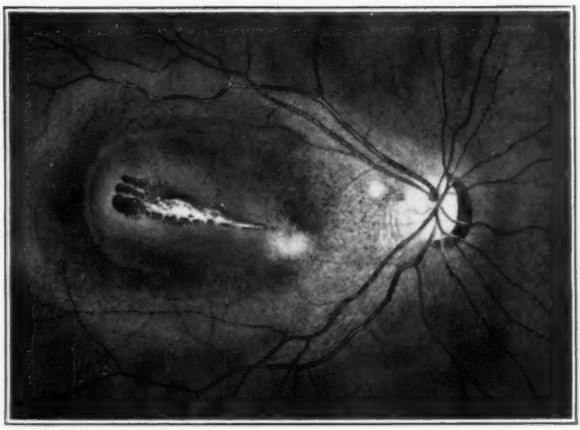

Fig. 3 (case 2).—The right eye.

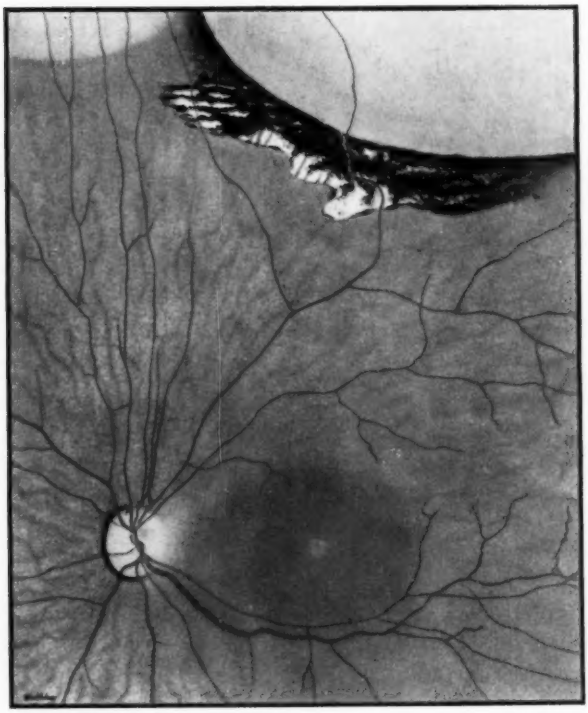

Fig. 4 (case 2).—The left eye.

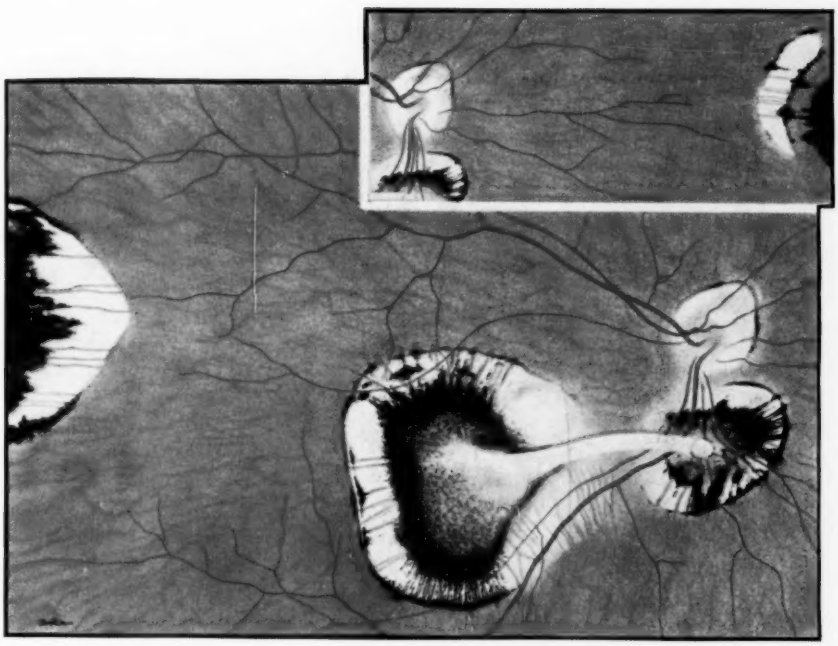

Fig. 5 (case 3).—The right eye.

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CASE 2 (Cowen, Wolf and Paige[4c]).—J. F., a boy, had jaundice at birth. There was enlargement of the liver and spleen. Internal hydrocephalus and intracerebral calcification were noted at the age of 26 days. Retardation of psychomotor development was pronounced. Bilateral chorioretinitis was observed at the age of 31 days.

Ophthalmologic Examination.—The visual acuity was impossible to evaluate with any certainty on repeated attempts; however, the eyes were attracted to, and readily followed, a blinking of light during the first three months of life, after which central vision was shown on similar testing to have decreased, although peripheral vision appeared to have been retained. Normal convergence ability was never demonstrated, but ocular motility and conjugate movements were well performed at the earlier examinations. Searching nystagmus became increasingly manifest after it first was observed, at the age of 3 months, at about which time there also developed esotropia, which progressed to 25 to 30 degrees for both near and distant fixation. Limitation of abduction in both eyes became evident gradually but at the end of the tenth month was so pronounced on the right that there was complete inability to abduct the right eye beyond the midline. The left was the dominant and fixing eye. Light perception in both eyes remained essentially normal on gross testing.

Externally, the right eye appeared normal at all examinations, and the structures of its anterior segment exhibited no abnormalities. The cornea was 11 mm. in horizontal diameter. A naevus flammeus 6 mm. in diameter appeared on the outer third of the left upper lid and brow two weeks after delivery. This increased in size to approximately 10 mm. during the ensuing months. The palpebral fissure of the left eye was normal and equal to that of the right, but the left cornea measured only a scant 10 mm. in its horizontal diameter. The anterior chamber of the left eye was questionably more shallow than normal, and there were numerous complete bands as well as some incomplete remnants of the pupillary membrane. Both pupils were round, normally situated and equally and promptly reactive consensually as well as directly to light, but the pupil of the left eye was slightly smaller than that of the right. This relationship continued throughout all subsequent examinations; however, both pupils increased nearly 1 mm. in diameter, and their reactions were not elicited as promptly as before. Synechias were not demonstrated at any time during mydriasis, but dilatation of the left pupil was never achieved as completely as that of the right, although both pupils remained normally round. Corneal astigmatism of moderate degree, as well as posterior lenticonus, was present in the left eye. None of the ocular abnormalities presented appreciable alterations in appearance, other than the changes already mentioned, on subsequent examinations.

Satisfactory ophthalmoscopic examination was not achieved on routine examination twenty-eight hours after delivery; however, both disks exhibited mild edema temporally, and this was more marked on the right. No hemorrhages were observed, nor were the abnormalities commented on at this time. The first of numerous subsequent examinations during infancy was done at the age of 31 days, only after adequate mydriasis had been obtained.

Ophthalmoscopically, a rather wide annular choroidal pigment ring about the disk of the right eye was partially obscured by low grade edema of the temporal

portion of the disk. The disk exhibited slight hyperemia but no measurable elevation. The retinal and choroidal vasculature and the retina itself were essentially normal except for a large egg-shaped, macular lesion, the small end of which was directed toward the disk. This lesion did not extend beyond the zone delimited by the main macular branches of the superior and inferior temporal arterioles and veins. The lesion was not altogether sharply defined, but its temporal end was partially demarcated by deep retinal granular brown-gray pigmentation of moderate density. This decreased gradually and within the length of 1 disk diameter vanished from view in the adjacent normal portion of the retina. This pigmentation was also seen along the margins of the remainder of the lesion and extended nasally to the temporal border of the disk, with progressively decreasing density and granularity; in addition, it became irregularly mosaic in pattern and rather reddish brown in color. The entire extent of the lesion, including the most peripheral pigmentation, was approximately 6 disk diameters in the horizontal and 3½ in the vertical axis. The central ovoid area outlined by more intense pigmentation measured 4 disk diameters horizontally and 2½ disk diameters vertically and was elevated slightly more than 1 D. centrally at its flattened apex. The presence of edema and hyperemia throughout the lesion proper was suggested by its homogeneous appearance, its lack of discernible normal granular central retinal detail and its dark, reddish blue–brown color. There was some centrifugally distributed, fine to moderately coarse reddish brown pigment, of greater density marginally, which was deeply situated within the retina over the lesion proper. An ill defined area near the temporal end of the lesion was pale and blue-gray in color. This partially capped the broader and temporal end of a long, roughly triangular area of chorioretinitis, irregularly outlined by pigment and situated centrally and nearly horizontally in the lesion itself. The narrow nasal end of this central triangular zone was pointed toward the disk and slightly downward, and at its border there were clumps of brown and deeply situated black pigment, heavier inferiorly and temporally. The pigment surrounded a roughly spindle-shaped, refractile white area which suggested that chorioretinal atrophy already had occurred and that the sclera had become visible (fig. 3).

Two small blurred dull, pale yellow juxtapapillary focal chorioretinal lesions were observed. The larger of these was ⅓ disk diameter in size and was situated within the egg-shaped lesion proper just below the apex of its nasal end. The smaller focal area was one half the size of the larger and was just off the disk margin in the 10 o'clock meridian. The nasal, or smaller, end of the egg-shaped lesion was a little more than 1 disk diameter from the temporal margin of the disk. The intervening retina appeared to be involved actively in the pathologic process, since structural detail was not discernible in this portion of the retina. Edema extended from the main lesion and seemed to involve also the papillomacular fiber bundle well onto the temporal sector of the disk and, thus, accounted for the blurred nerve head. Several small concentric curved glistening bands situated vertically just temporal to the disk margin suggested early glial tissue proliferation.

Examinations were made at irregular intervals during the ensuing nine months. The central chorioretinitis extended temporally at first and then superiorly and

inferiorly as well as nasally. At the end of the fifth month of life, the active process appeared to have subsided completely. The lesion at this time occupied the whole of the originally observed egg-shaped area. Irregularly distributed, rather dense, dark brown and black pigment varying from moderately fine to coarsely granular was diffusely interspersed with unevenly proliferated pale connective tissue. A band of black pigment of varying width and thickness outlined the borders of the lesion and became less dense as it extended into the adjacent portion of the retina for a distance of about 1 disk diameter. The two focal juxtapapillary lesions noted originally were no longer identifiable separately. A few fine or broad deep retinal bands of pale connective tissue extended into the disk temporally. The disk exhibited moderate loss of nerve substance in its temporal half and pronounced generalized pallor. Occasional short, apparently normal, retinal vascular twigs traversed the periphery of the lesion for short distances. Further inflammatory activity was not observed during the remainder of the year of infancy; however, further scarring occurred with increasing pigmentation. Optic pallor and atrophy became somewhat more manifest during this period. The retina otherwise remained essentially normal. The media were clear on each examination.

Ophthalmoscopic visualization of the left eye was difficult because of an astigmatic refractive error and a posterior lenticonus. The first satisfactory view was obtained with the eye under mydriasis at the age of 31 days, at which time the disk was essentially normal in color except for slight hyperemia. It was not elevated, but low grade edema of its temporal portion partially obscured a narrow complete choroidal pigment ring. The retinal and the choroidal vasculature as well as the retina itself were normal except for a large poorly demarcated ovoid macular lesion 2 D. elevated. Two large, old chorioretinal lesions that had escaped earlier observation were seen in the extreme periphery superiorly on a subsequent examination at the age of 46 days. The macular lesion was confined to the central area and was bounded circumferentially by the superior and the inferior temporal arterioles and their lateral macular branches. The area measured 3½ disk diameters vertically, and its temporal margin was 4½ disk diameters from the mildly edematous temporal margin of the optic disk. The intervening portion of the retina was also edematous. The lesion was homogeneous in appearance in spite of the slight granularity of its surface. Its dull, deep, reddish blue–brown color diminished gradually to merge into the adjacent normal portion of the retina; centrally, however, in the flattened apex of the lesion, there was a slightly orange-brown shallow round umbilication measuring ¼ disk diameter that appeared to approximate the foveal area in location (fig. 4).

Numerous reexaminations during the ensuing nine months revealed that the entire macular area was the site of pigment deposition, chorioretinal atrophy and connective tissue proliferation. The lesion in the main was similar to that in the right macular region but lagged behind it in development by one month. Inflammation appeared to have subsided completely at the end of the sixth month of life. The appearance of the left disk ultimately closely approached that of the right.

The far periphery of the large lesions found superiorly could not be delimited. These areas appeared to be elevated, since the few retinal vessels present seemed to arch forward as they coursed upward. The inferior margins of both lesions were rounded, with the convexity directed downward. The smaller lesion was barely discernible, since it was situated so far superiorly that its inferior margin was approximately 9 disk diameters above the upper margin of the disk of the

left eye. It was well demarcated because of its dull, pale gray-green color, but neither the body of the lesion nor its margins exhibited any pigmentation. The larger lesion was a dull aquamarine in color and was defined sharply by many small black clumps of pigment that extended outward and downward across an irregularly serrated band of old, healed chorioretinitis with atrophy. This band was directed inferonasally and did not exceed 1½ disk diameters in extent. Its superonasal and inferotemporal extremities also were pigmented but did not exhibit chorioretinal atrophy. No evidence of inflammatory or of further degenerative activity was observed in these two lesions at any time. It was believed that each lesion probably represented smooth and rounded masses of nonpigmented proliferated connective tissue, the color of which could not be explained. The media constantly remained clear.

Case 3 (Cowen, Wolf and Paige [4c]).—A. I., a boy aged 2 years, was jaundiced on the fourth day of life. He had a diffuse maculopapular rash, which lasted until the fourth week of life. The liver and spleen were palpable. Intracerebral calcification appeared at 7 weeks. Microcephalus was noted at 5 months. Speech was defective. A central chorioretinal lesion was observed in each eye at 2 years.

Ophthalmologic Examination.—The visual acuity of each eye was poor, since only relatively large objects, such as a rattle or colored blocks, were seen when held within arm's distance of either eye. Larger moving objects apparently were not observed beyond 6 feet (183 cm.). The light perception of each eye seemed to be normal on gross testing. There was an alternating convergent strabismus of approximately 40 degrees of arc. The left eye was questionably dominant. The pupils were normal on inspection but reacted only sluggishly to direct light, to consensual testing and on accommodation-convergence stimulation.

Ophthalmoscopically, the optic papilla of the right eye exhibited the dirty gray-white generalized pallor characteristic of optic nerve atrophy consecutive to edema of the disk. This observation was confirmed by the presence over its surface of irregular tissue proliferation with fine short stellate perivascular and peripapillary extensions, particularly inferotemporally. The superior and the nasal margin of the disk were also slightly obscured by this process, and some mild gray-black marginal pigmentation was present. The retinal vasculature exhibited mild smooth generalized narrowing (fig. 5).

There were five large old, healed areas of chorioretinitis, horizontally arranged, in the posterior third of the fundus. These lesions were essentially rounded or ovoid and varied in size from 2 to 6 disk diameters. There was no apparent evidence of inflammatory activity, and all were pigmented in varying degree. Each exhibited atrophy of the choroid and retina, and attenuated deep choroidal arteries traversed their bases. Connective tissue proliferation was present in each to some degree. The most striking example of this was a thick forward-arching band that bridged an isthmus of questionably normal retina between two large lesions immediately inferotemporal to the disk. There was pronounced extensive irregular gray to black pigment deposition. This pigmentation accentuated the punched-out appearance of each lesion, in the center of which there was proliferated connective tissue containing pigment. Local tissue proliferation, however, was absent in a crescentic area situated approximately 6 disk diameters from the nasal margin of the disk, although nasal to that there was a lesion with marked pigment deposition and tissue proliferation.

Ophthalmoscopically, the left eye was similar to the right. The optic disk also exhibited secondary optic nerve atrophy, and all of its margin except a slight

nasal choroidal pigment crescent was entirely obscured by secondary glial tissue proliferation. Temporally, and arising from the disk margin, there was a low wide crescentic slightly elevated area, over the gray-brown granular surface of which normal retinal capillaries coursed toward the nasal portion of the macular area. The part of the retina and the choroid between the disk and the macular region exhibited numerous minute nearly parallel furrows, the long axes of which were directed inferotemporally and appeared to converge toward the ill defined superotemporal borders of a large area of old, healed chorioretinitis. This was situated immediately below the optic disk and appeared to be joined temporally

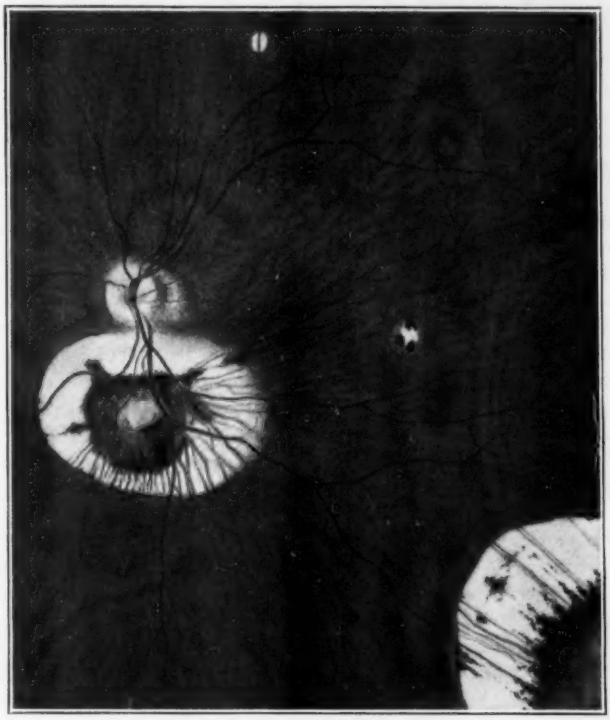

Fig. 6 (case 3).—The left eye.

to the disk with fine connective tissue bands that emanated from a large area of proliferated connective tissue in the center of the lesion. Inferotemporal to the disk and deep within the inferotemporal quadrant there was a large similar lesion. Both of these areas were sharply defined and showed large central areas of connective tissue proliferation heavily infiltrated with black pigment. Numerous attenuated choroidal arteries traversed the readily observed, glistening sclera. These two lesions were ovoid and were 3 and 8 disk diameters, respectively, in size. One of two small similar areas, less than ½ disk diameter in extent, occupied most of the left macular area and completely obliterated the foveal region, while the other, smaller, poorly defined atrophic lesion was situated nearly 6 disk diameters above the disk along the 1 o'clock meridian. The former exhibited irregular heavy black pigmentation, together with complete chorioretinal atrophy,

in contrast to the lack of pigment in the latter. The retinal vasculature in general was mildly but smoothly attenuated in caliber. The remainder of the retina and of the choroid were normal. No changes were observed in the appearance of the lesions during the period of hospitalization. The media remained clear (fig. 6).

CASE 4 (Cowen, Wolf and Paige [4c]).—M. B., a girl aged 4 years, had left internal strabismus, noted at about the age of 2 months; defective speech, noted at the age of 4 years; intracerebral calcification; microphthalmos on the left side, and bilateral focal chorioretinitis.

Ophthalmologic Examination.—Numerous ocular examinations were conducted at irregular intervals throughout the seven months during which the patient was under observation. Her parents stated that her vision always had been poor and that the left eye seemed smaller than the right and tended to deviate inward, particularly on fatigue. The visual acuity could not be determined with accuracy, although common small objects as well as larger distant moving objects appeared to be recognized fairly well with either eye. Slight improvement was obtained with temporary corrective lenses after retinoscopy, which revealed a relatively high degree of compound hyperopic astigmatism in both eyes.

Externally, the linear measurements of the right eye were normal, since the cornea, the palpebral fissure and the pupillary aperture, respectively, measured 11 mm. horizontally, 7.5 mm. vertically and 3 to 4 mm. in diameter; however, the same structures in the left eye measured 7.5 mm., 6 mm. and 5 mm., respectively. Both pupils reacted moderately well to the usual stimuli, but the response of the right was somewhat more prompt than that of the left. The monocular motility of both eyes was normal, but for near and for distant fixation there was esotropia of 30 and 35 prism diopters, respectively, as estimated with the Hirschberg corneal reflex test. The right eye constantly was the dominant, or fixing, eye. Biomicroscopy was not feasible, but a few remnants of pupillary membrane were revealed on examination with the hand loupe. These observations remained unchanged during the entire period of observation.

Ophthalmoscopically, the optic disk, the retina and the retinal and choroidal vasculature of the right eye were essentially normal except for a somewhat jaggedly marginated, roughly triangular, heavily pigmented old healed chorioretinal lesion situated immediately temporal to the macular area. The apex was directed nasalward in the horizontal axis, and the base was temporal and horizontal. There were a number of fine parallel superficial connective tissue bands in the retina that seemed to connect the apex of the lesion with the fovea proper. The sclera was partially and irregularly visible throughout the lesion, which exhibited little connective tissue proliferation but showed heavy gray-black pigment deposition. This pigmentation raggedly delimited the margins of the lesion, which was little more than 1 disk diameter in any dimension. The media were clear.

Ophthalmoscopically, a very small posterior cortical cataract was observed in the left eye, the presence of which was confirmed with the hand loupe. Visualization of the fundus was further hindered because of numerous fine to moderately coarse opacities of the vitreous. The optic disk showed moderate generalized pallor, and there was questionable loss of substance in its temporal half. There was a large ovoid healed nonproliferative but pigmented chorioretinal lesion in the extreme periphery of the upper temporal quadrant. Its long axis was approximately 3 disk diameters and was directed obliquely upward in the 1 o'clock meridian. There was much irregular heavy gray-black pigment deposition in this lesion, which appeared to have resulted from the coalescence of five similar, smaller

lesions. Occasional islands of sclera, together with attenuated deep choroidal arteries, were observed in the base of the large area. There was no observable local inflammatory activity. The macular area appeared to be normal except for minimal thickening and the absence of a foveal reflex. There was a large pale blue-grayish white, roughly triangular area in the upper nasal quadrant. The blunt apex was 1 disk diameter from the superonasal margin of the disk. The far periphery of this large lesion could not be delimited and was elevated 2 to 4 D. more than its central portion, which was elevated 3 to 4 D. The surface of the lesion, over which no retinal vessels were seen, was more coarsely granular peripherally, and there was complete absence of minute detail. The visible margin of this large area, which occupied most of the upper nasal quadrant, was demarcated by a narrow band of finely granular gray-black deep and superficial retinal pigment. Immediately peripheral to the pigment band, there were approximately a dozen small whitish deep retinal exudates of chronic edema, a few of which were also found just within the lesion proper. The retina at the margins of the visible segment of the lesion exhibited slight haziness of structural detail for approximately the width of 1 disk diameter. This was believed to represent local low grade retinal edema, probably indicative of an active inflammatory process, perhaps accounting for the wider pupil and the opacities in the vitreous of the left eye. No appreciable changes in the lesions, however, occurred during the period of observation.

CASE 5 (Cowen, Wolf and Paige [4c]).—D. H., a Negro boy aged 11 years, had left external strabismus and "congenital eye lesions," noted at the age of 4 years; petit mal attacks, which began at 7 years; a small area of calcification in the brain and old healed bilateral chorioretinitis, noted at 11 years, and subnormal intelligence.

Ophthalmologic Examination.—The visual acuity, which had always been poor, was 20/100 in the right eye and 1/200 in the left both with and without correction. The patient was able to spell out the words of the no. 8 Jaeger test type at 5 inches (13 cm.) without glasses. Retinoscopy revealed mild compound hyperopic astigmatism in the right eye and severe compound myopic astigmatism in the left eye; however, the visual acuity could not be improved with any corrective lenses. Externally, no abnormalities were noted except left exotropia of one year's duration. This measured 15 and 20 degrees of arc for distant and for near fixation, respectively. The monocular motility appeared to be unimpaired except for fine searching nystagmus of both eyes. The peripheral visual fields were normal on gross testing. The pupils were normal, round and equal and reacted moderately well to the usual stimuli, although the response of the left was less prompt than that of the right. No other inequalities or abnormalities were observed in either eye.

Ophthalmoscopically, there was moderate temporal pallor of the optic disk of the right eye, but no atrophy was discernible. The nerve head was clearly defined and exhibited shallow physiologic excavation. The retinal vasculature was normal. Centrally, there was a large rather stippled ovoid diffusely pigmented old healed chorioretinal lesion. Its long axis was horizontal and measured approximately 3 disk diameters in length. The superior margin of the lesion was level with the lower pole of the disk, while the superonasal margin was 1½ disk diameters obliquely and temporally downward from the inferotemporal border of the disk. The lesion was demarcated sharply by marginal deposition of black and brownish black deep and superficial pigment. Pigmentation was also present throughout the lesion in an eccentrically distributed mosaic pattern, so that the

sclera was visible in isolated patches, indicative of the presence of chorioretinal atrophy. Occasional segments of narrow choroidal arteries were seen in the depth of the lesion. Some slight uneven low grade pigmented connective tissue proliferation was also present. Above and below the temporal periphery of the large central lesion there were several similar, but much smaller, areas (½ disk diameter in size) of old healed chorioretinitis. A few short apparently normal fine retinal vessels extended into the margins of the large and some of the smaller lesions. The media were clear.

The lesions observed in the left eye were similar ophthalmoscopically to those in the right eye but were slightly more pronounced and the pallor of the temporal portion of the disk was somewhat more intense. The media remained clear.

Case 6 (Cowen, Wolf and Paige [4c]).—C. J., a boy aged 7 years and 6 months, had defective vision; "twitching of the eyes"; intermittent right internal strabismus, noted at the age of 3 months; virtual blindness in the right eye, noted at 1 year; generalized convulsive seizures, which began at 18 months, and old central bilateral chorioretinitis, noted at 7 years and 6 months. An electroencephalogram showed diffuse pathologic changes.

Ophthalmologic Examination.—The patient was under observation for fifteen months after his first registration at the clinic. The visual acuity ("E" chart) without correction was 10/200 in the right and 18/200 in the left eye. Apparently spontaneous improvement to 18/200 and 20/200, respectively without correction, occurred after attendance for an academic year in a school for the blind. Externally, there were no manifest abnormalities; however, the cornea of each eye measured a scant 10.5 mm. in horizontal diameter. The pupils were normally situated, round and 5 mm. in diameter. They reacted equally but only moderately promptly to the usual stimuli. The monocular motility was normal for both eyes, but there was searching rotatory nystagmus with inability to fix with either eye, although the left occasionally appeared to be the more dominant. The right eye deviated inward to 25 degrees of arc both for near and for distant fixation. Biomicroscopy gave essentially negative results. No appreciable external or internal ophthalmologic changes were noted on subsequent examinations.

Ophthalmoscopically, severe generalized pallor and atrophy of the right optic papilla were observed; however, a small horizontal nasal sector was slightly pinkish. Centrally there was a large round partially proliferative and diffusely pigmented area of old healed chorioretinitis. This completely obliterated the macular region and measured approximately 4 disk diameters. Its nasal margin was 2 disk diameters from the temporal border of the disk. Islands of yellowish white glistening sclera were partially visible throughout the lesion. A few narrowed straight choroidal arteries were observed deep in the base of each of these small areas. There was diffuse but irregularly distributed deep and superficial heavy black pigment deposition, much of which was located peripherally and produced a sharp marginal definition of the area. A few small masses of connective tissue proliferation elevated to 2 D. caused refractile surface irregularities. Eight smaller lesions, similar to the large central one, were grouped in satellite fashion immediately peripheral to the main lesion. The majority of these, none of which exceeded ½ disk diameter in size, were situated above the horizontal diameter.

The lesions observed in the left eye were so similar to those in the right that they closely approximated mirror images of them.

OCULAR LESIONS IN PREVIOUSLY REPORTED CASES OF TOXOPLASMIC ENCEPHALOMYELITIS

Ophthalmoscopic observations fortunately had been made in 3 of the 5 cases observed in this clinic in which postmortem examination was performed [5]; however, the correct diagnosis had not been made before death in these instances, so that attention was not directed particularly to the eyes, and the clinical descriptions of the lesions consequently were brief.

J. S. (Wolf and Cowen [4a]), a white girl aged 24 days, had convulsions, slight enlargement of the head, enlargement and bulging of the anterior fontanel, retraction of the head, twitching movements of the extremities and hyperactivity of the deep reflexes. The Babinski sign was present on both sides. The pupils reacted sluggishly to light. The cerebrospinal fluid was xanthochromic, with a high protein content and pleocytosis. The infant died at 30 days.

At the age of 28 days the media were clear ophthalmoscopically. There was an elongated yellowish white area about 4 disk diameters in size in the upper nasal quadrant of the retina of the right eye. Retinal vessels were seen on its surface, and there were no hemorrhages. Temporal to this area there was a zone of choroidal atrophy with pigment clumping about 2 disk diameters in size. The vitreous of the left eye was hazy and did not permit adequate examination of a large yellowish white avascular area in the periphery of the retina.

It was the final consensus clinically that the elevated areas in the retina were of inflammatory origin; however, glioma of the retina with invasion of the brain was considered a diagnostic possibility.

C. D. (Wolf, Cowen and Paige [1b]), a white boy, had convulsions on the third postnatal day. Horner's syndrome on the left side, deviation of the eyes to the right and nystagmus to the right were present. Retraction of the head appeared on the seventeenth day. Progressive high cervical transverse myelitis was complete in the fourth week of life. The body temperature was labile. The cerebrospinal fluid was xanthochromic. The patient died at 31 days.

Ophthalmoscopic examination revealed an irregular reddish brown area in each macular region. Each area measured approximately 1 disk diameter in size, but that on the right was somewhat smaller than that on the left.

The clinical impression was that the intraocular lesions represented retinal hemorrhages associated with multiple injuries of the central nervous system sustained in the course of delivery. Compression of the cervical portion of the spinal cord by a hematoma was also considered.

L. M. (Paige, Cowen and Wolf [4b]), a white girl who was slightly premature, had hydrocephalus at birth. Small shadows of calcium density in the brain were demonstrated by roentgenograms on the sixth day. There was xanthochromic cerebrospinal fluid with a high protein content. The hydrocephalus was progressive, with terminal convulsions. The temperature was subnormal. The child died at 9 weeks.

Both eyes were smaller than normal according to the size of the corneas, which measured 7 to 8 mm. in horizontal diameter. Nystagmoid movements were observed, and there was limitation of lateral gaze to the left. The pupils were fixed in response to direct light. A few relatively large vessels were observed anteriorly in each iris.

Ophthalmoscopically, a pinkish reflex was obtained from each fundus, which was obscured by a large apparently vascularized "membranous mass" posterior to each lens.

Clinically, diagnoses of obstructive hydrocephalus and congenital microphthalmos were made. Retinal detachment, persistent tunica vasculosa lentis and glioma of the retina were also considered.

Jankû's [7] case, which is of particular interest, was reported as an instance of unidentified sporozoon infection of the eyes. It was reclassified at a later date as a case of infantile toxoplasmic encephalomyelitis.[8] The patient was a boy born after a normal pregnancy and labor. Blindness was noted at the age of 3 months. There was progressive hydrocephalus, with death at 16 (?) months.

The left eye was smaller than the right, and the extraocular movements were limited to upward gaze and could be performed only slowly. Ophthalmoscopically, there was a large oval horizontally elongated lesion in the macular region of the right eye. It was 3 by 2 disk diameters in size and was distinctly marginated by a band of dark finely granular pigment. It was atrophic and slightly concave. There was a yellowish zone just internal to the pigmented border and merging into the white of the atrophy proper. Some reddish choroidal vessels were seen in the yellow zone. There was black pigment interspersed with grayish white tissue running horizontally and nasally in the papillary portion of the lesion. The retinal vessels were absent in this region. The nerve head was vertically oval, blurred, grayish white and slightly elevated, and its vessels were small in caliber.

There were grayish blue reflexes that extended from the extreme nasal periphery of the retina of the left eye to its macular region, where there was a white atrophic area about 2½ by 5 disk diameters in size. This was outlined by black pigment deposition. The retinal surface nasally simulated that observed in advanced retinal detachment or in intraocular tumor. The atrophic zone in the macular region was depressed centrally and was yellowish white, with reddish streaks near the margins and specks of pigment increasing in number toward the periphery. No retinal vessels were visible in the central area of chorioretinal atrophy. The optic papilla was elevated and grayish, and the temporal margin was not discernible.

PATHOLOGIC OBSERVATIONS IN TOXOPLASMIC CHORIORETINITIS

The posterior halves of the eyes were examined histologically in 4 of the 5 cases of toxoplasmic encephalomyelitis observed in this clinic in which autopsy was performed. The eyes exhibited relatively active, moderately early chorioretinal lesions in 3 instances, the cases of J. S.,[4a] C. D.[1b] and B. R.[4b] Two of the children (J. S. and C. D.) were about a month old at death, and the third (B. R.) was stillborn. The fourth infant (L. M.[4b]) died at the age of 9 weeks and showed relatively inactive, more chronic lesions. No opportunity has been afforded as yet for histologic study of either the earliest or the healed, later stages of this infection in the eye.

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7. Jankû, J.: Parasites in Coloboma of the Macula, Časop. lék. česk. **62**:1021-1027, 1054-1059, 1081-1085, 1111-1115 and 1138-1143, 1923.

In the earlier lesions observed in 3 of the infants the pathologic changes observed were as follows:

Focal areas of swelling of the retina were seen (fig. 7). In these zones there were intense edema, congestion, distortion of the retinal lamination and varying degrees of necrosis and inflammation. Congestion and edema usually involved all the layers, but were more intense at times in the inner three layers. Necrosis of all the retinal laminas occurred in the more central portions of the lesions; however, only the inner layers were degenerated in some instances. Normal

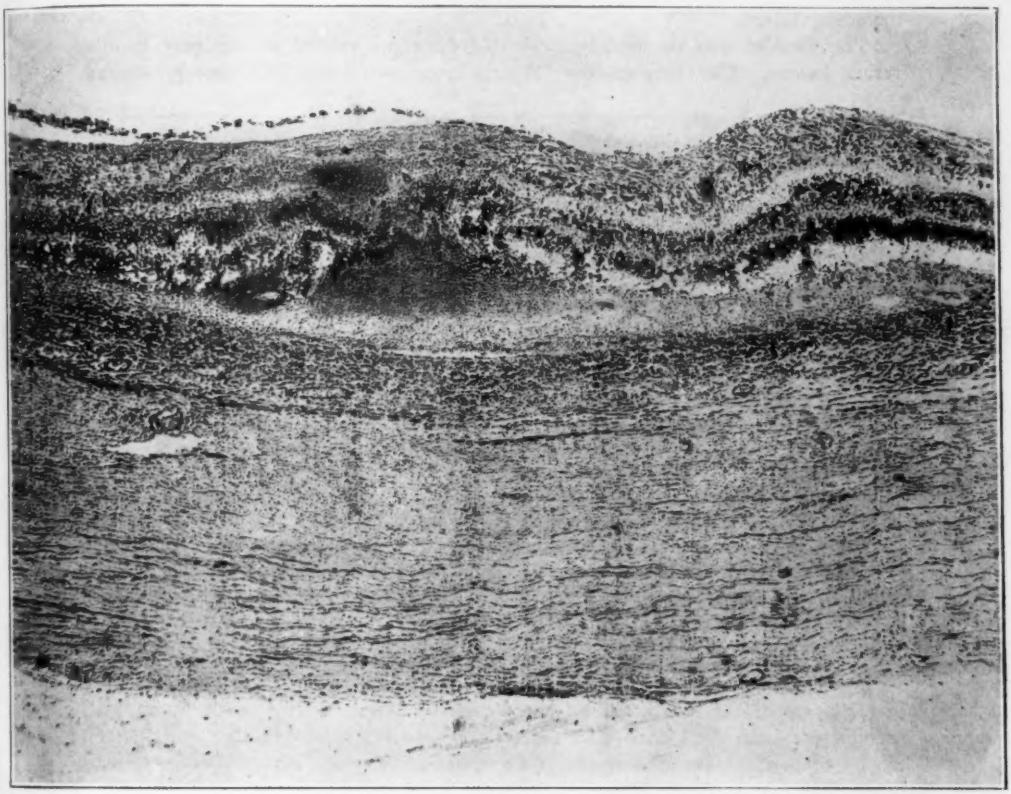

Fig. 7 (J. S.).—Focal toxoplasmic chorioretinitis, left eye, showing necrosis in the retina with disruption of its architecture and dense infiltration of the choroid (phloxin-hematoxylin stain).

structures were replaced by amorphous cytoplasmic and nuclear debris (figs. 7 and 8). Perivascular and diffuse infiltration by lymphocytes, plasma cells and occasional eosinophils and lipoid-laden phagocytes was present, chiefly at the marginal zones of the necrotic areas (fig. 9*B*). In some lesions, polymorphonuclear leukocytes were also observed. Endothelial hyperplasia of the capillaries occurred. Small amounts of exudate, similar to those observed in the retina, could be found on the free surface of the internal limiting membrane and were

often associated with an ingrowth of fibroblasts and capillaries into the vitreous. This loose-meshed granulation tissue did not extend deeply into the vitreous at this stage. At the margins of the necrotic zones where partial degeneration had occurred, displacement of cells of one layer into another resulted in considerable distortion of the retinal architecture (fig. 8). Cells of the nuclear layers were frequently dislocated, and the retinal pigment layer, which was at times hypertrophied, was often disrupted, with discharge of free pigment and displacement of pigmented cells into the inner retinal layers (fig. 8). The majority of the nerve cells of the ganglionic layer had disappeared. Edema was often most intense in the loose-meshed stratum opticum and in the ganglionic and inner molecular layers.

The choroid was moderately infiltrated in areas related or adjacent to the retinal lesions. The choriocapillary layer was congested and infiltrated by plasma

Fig. 8 (B. R.).—Focal toxoplasmic chorioretinitis, right eye, showing necrosis of all layers of the retina, diffuse chronic inflammation, disruption of the retinal architecture with displacement of the cells of one layer into another and hypertrophy of pigmented epithelium with dispersion of pigment into the inner retinal layers (phloxin-hematoxylin stain).

cells, lymphocytes and eosinophils. Some of the capillaries showed endothelial hyperplasia. A less dense cellular exudate and edema were present in some portions of the lamina vasculosa. The sclera was normal. The leptomeningeal sheaths of the optic nerve were mildly or moderately infiltrated by cells similar to those seen in the choroid, and in a nerve in which the process had extended focally along the vessels and septums into the parenchyma, lipoid-laden phagocytes were also present.

The inflammation was less pronounced and astrocytosis and capillary hyperplasia were fairly prominent in the 1 instance in which the lesions were somewhat more chronic (fig. 9 *C*). The outgrowth of granulation tissue into the vitreous was extensive (fig. 9 *A*).

Toxoplasmas were present in the retinal lesions and in general were most frequent where the lesions were most severe. Occasional parasites without accompanying reaction were observed in relatively normal portions of retina near the margins of inflammatory foci. They occurred singly or in clusters, free or intracellularly or as "cysts." They were rare in the choroid. Details of their morphologic and biologic characteristics can be found in previous papers of this series.[1b]

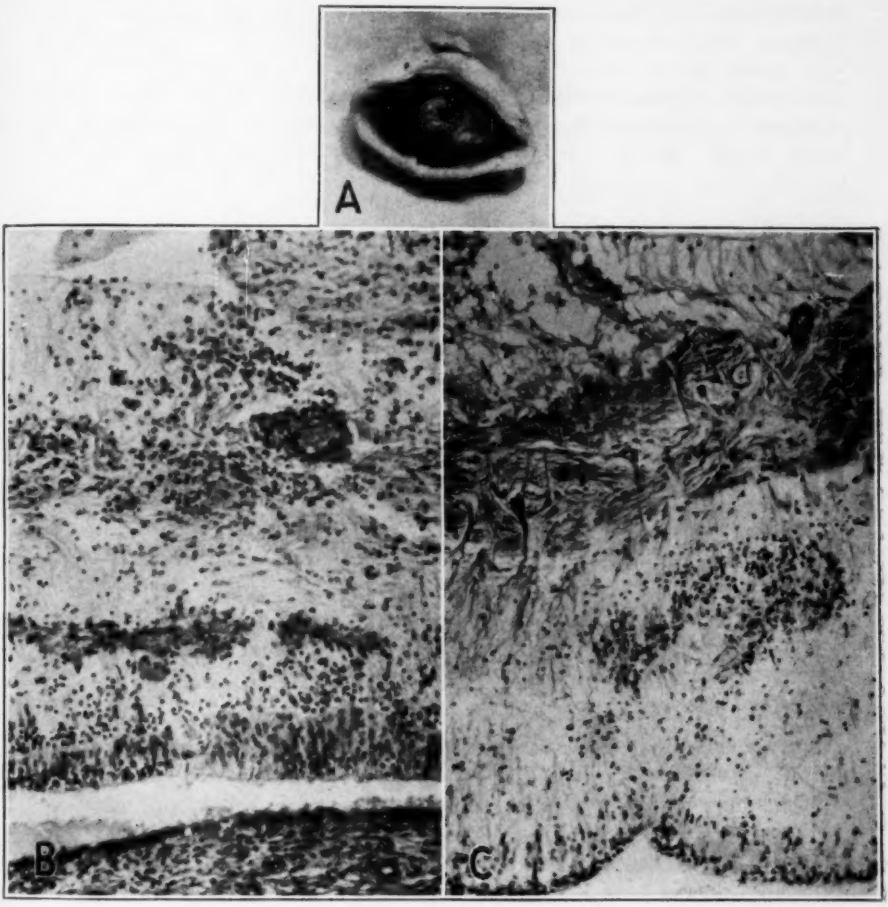

Fig. 9 (L. M.).—Toxoplasmic chorioretinitis, left eye. *A*, note the mass of partially organized granulation tissue extending into the vitreous from the retina. *B*, disorganization of the retina with perivascular and diffuse infiltration by lymphocytes and large mononuclear cells and mild lymphocytic infiltration of the choroid (phloxin-hematoxylin stain). *C*, pronounced disorganization of the retina due to degeneration of retinal elements (phloxin-hematoxylin stain). Note the intense gliosis forming a dense transverse band in the inner layers.

The accompanying photomicrographs illustrate the appearance of these parasites in the retina (fig. 10).

The pathologic changes in the eyes in Jankû's case, previously referred to, were as follows:

There were macular lesions in each eye which seemed to be much older than those in the eyes of the 4 infants described. The central portion of the lesions showed the severest changes. The inner nuclear, molecular and ganglionic layers were thinned out, showed an increase of glial tissue and were invaded by newly formed connective tissue and pigmented epithelial cells. The internal limiting membrane was destroyed in places, and clumps of hyaline and granular material were present on the internal surface of the retina. The pigmented layer of the retina was frequently disrupted and was depigmented in places. Often islands of disrupted, hypertrophied pigmented epithelium extended into the rest of the retinal tissue, forming large clusters of finely granular dark brown or black pigment. The hyperplastic choriocapillary layer and the intermediate stratum

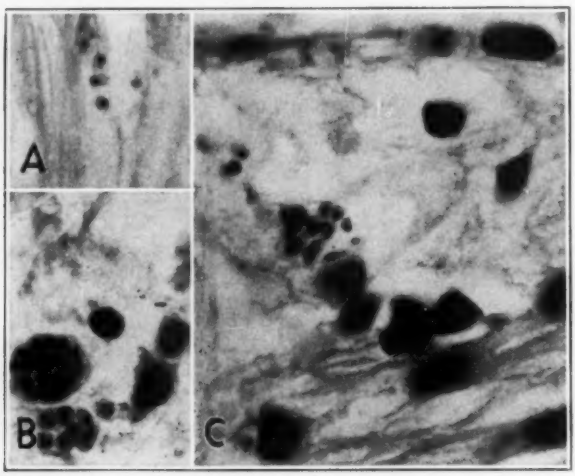

Fig. 10 (J. S.).—Toxoplasmas in retinal lesions, left eye. *A*, single extracellular toxoplasmas (phloxin-hematoxylin stain). *B*, clusters, or "cysts," of toxoplasmas in degenerated retina (phloxin-hematoxylin stain). *C*, group of extracellular toxoplasmas (hematoxylin and eosin stain).

of the choroid had proliferated fanwise into the retina through defects in the pigmented epithelial layer and the lamina basalis. The connective tissue trabeculae surrounded the masses of displaced pigmented epithelium. Small amounts of retinal pigment were displaced into the choroid as well. Toward the margins of the lesions where the changes were less intense, the retinal architecture was disturbed owing to disruption and displacement of many of the layers. The choroid was congested and showed perivascular lymphocytic infiltration. Near the severer retinal lesions, the choriocapillary layer was obliterated by fibrosis and the remainder of the choroid was more vascular and more heavily infiltrated with lymphocytes.

The lesion in the left eye was somewhat more chronic than that in the right eye, since there were fewer inflammatory phenomena and more fibrosis and gliosis.

Relatively avascular glial tissue had replaced the layer of rods and cones at the edges of the lesion, while centrally it replaced all but the ganglionic layer. Jankû described a congenital malformation of the retina of the left eye on the temporal side of the ciliary body, consisting of a tumor-like hypertrophy of the retina without inflammatory changes. This eye was also microphthalmic.

Parasitic "cysts" were found in the lesion in the right eye only and were thought by the author to be some form of sporozoon. Later reevaluation of this case by Levaditi and associates[9] and by us[8] left little doubt that these organisms were toxoplasmas.

TOXOPLASMIC CHORIORETINITIS IN THE COMMON FOWL

It is of interest that spontaneous toxoplasmic chorioretinitis similar to that observed in man has been reported in the common fowl by Hepding.[10] To our knowledge, spontaneous toxoplasmic chorioretinitis has not been reported in other animals. Levaditi and associates have produced experimental ocular toxoplasmosis in rabbits.[9] Hepding described a cock with mild catarrhal symptoms in the upper respiratory tract in which slight chemosis and tearing of the left eye developed. The cornea became slightly cloudy, and during two months of observation the bird became emaciated but paralysis did not develop. Only the left eye was examined histologically. It showed a widespread necrosis of the retina about the optic nerve. All the retinal layers were involved, and although lamination was still visible, histologic details could not be made out. Smaller foci of necrosis were scattered through the less severely involved middle third of the retina. The retina at its junction with the pars ciliaris was infiltrated by large mononuclear cells. Some swollen large mononuclear cells and fibrin were present just anterior to the internal limiting membrane. The optic nerve at its point of entrance into the globe was intensely infiltrated by round cells and invaded by fibroblasts. The uveal tract was congested and infiltrated by lymphocytes and plasma cells. Perivascular infiltration was present in the extraocular muscles and in the periorbital fat. Toxoplasmas singly and as cysts were found in the lesions.

PATHOGENESIS OF OCULAR LESIONS

The evidence for the fetal inception of infantile toxoplasmosis has been presented in earlier publications in this series.[11] In brief, the

8. Wolf, Cowen and Paige (footnote 1 *a* and *b*). Wolf and Cowen.[4a]

9. Levaditi, C.; Schoen, R., and Sanchis-Bayarri, V.: L'infection toxoplasmique expérimentale de l'œil, Compt. rend. Soc. de biol. **98**:1414-1419 (May 21) 1928.

10. Hepding, L.: Ueber Toxoplasmen (Toxoplasma gallinarum n. sp.) in der Retina eines Hühnes und über deren Beziehung zur Hühnerlähmung, Ztschr. f. Infektionskr. **54-55**:109-116, 1938-1939.

11. Wolf, A.; Cowen, D., and Paige, B. H.: Fetal Encephalomyelitis: Prenatal Inception of Infantile Toxoplasmosis, Science **93**:548-549 (June 6) 1941. Paige, Cowen and Wolf.[4b]

reasons were the onset of symptoms at or soon after birth and pathologic evidence that lesions were present before birth. The occurrence of microphthalmos and of other congenital ocular defects in association with the toxoplasmic chorioretinitis tends to support this view. It seems likely that the presence of the infection of the eye during intrauterine life interferes with its normal development. The interference probably occurs late in gestation, since no major malformations of the eye or nervous system have been found.

Jankû said that his case was one of probable fetal infection by a parasite and compared the mode of infection to that in congenital syphilis. He stated the belief that the chief site of the inflammatory process was the choroid of the eye in the macular region. Reactive changes in the retina with destruction of its pigmented epithelium were associated with it.

As has been mentioned elsewhere,[4a] the parasite probably reaches the brain and other organs by way of the fetal circulation from the placenta. Although the evidence is strongest for this route of infection of the eyes, it is possible that the infection passes by way of the subarachnoid space in the optic nerve sheaths to the ocular bulbs after the brain has been infected. This, however, is not likely. Until the earliest stages of the chorioretinal infection are available for pathologic study, the initial site of infection of the eye cannot be stated with certainty.

EVOLUTION OF TOXOPLASMIC CHORIORETINITIS AS OBSERVED OPHTHALMOSCOPICALLY

The earliest lesion was that seen in the macular area of the left eye of J. F. (case 2). This acute lesion was characterized chiefly by localized edema, by indefinite demarcation, by early central necrosis that approximated the position of the fovea and by retention of the normal appearance of the retinal vasculature. A somewhat further developed lesion was seen in the macular area of the right eye of the same infant. This exhibited a lesser degree of edema, with a central chorioretinitis that was already moderately well advanced, particularly in the area corresponding to the fovea. In this central zone, chorioretinal atrophy was sufficiently advanced to permit visualization of the underlying sclera. Pigment clumps appeared at the border of the central atrophic area and were more diffusely granular in, and at the periphery of, the less edematous marginal zone. Two smaller, tubercle-like additional foci of atrophy and pigmentation at the nasal periphery of the main lesion were possibly less advanced.

The large, convexly curved lesion in the upper temporal quadrant of the left eye in the same patient was definitely older than the two just described and might be considered an example of a subacute lesion. This

was evidenced by sharp margination, lack of local edema and a band of irregular depressed old inactive pigmented chorioretinitis with atrophy at its borders. This protuberant area was singularly structureless and probably represented an avascular homogeneous fibrous mass which developed from granulation tissue that had invaded the vitreous.

A lesion in the upper nasal quadrant of the left eye in case 4 (that of M. B.) closely resembled the last lesion described and seemed to have reached the same stage of development except that numerous small marginal exudates of chronic edema were present in association with an ill defined band of bordering retinal edema suggesting a still active process or a recrudescence.

All the other chorioretinal lesions in the 6 cases as observed ophthalmoscopically were chronic and exhibited no activity. Essentially, they were sharply marginated areas of chorioretinal atrophy or proliferation, of varying degree, with diffuse irregular pigment deposition, more concentrated at the margins. The retinal vasculature remained surprisingly normal.

The vitreous in all but 1 of the twelve eyes observed (the left eye in case 4) remained constantly clear, and the retina was entirely normal except for the portions immediately adjacent to lesions in the very active stages.

Situation and Number of Lesions.—Multiple chorioretinal lesions, two to twelve in number, were observed in all the eyes examined except the left eye in case 2 and the left eye in case 1, each of which had only one lesion. In every instance there was a definite macular lesion, except for a small, doubtful area centrally in the left eye in case 4. The macular lesions were for the most part fairly large. The other lesions were either smaller satellite lesions or large areas in the relatively far periphery.

ASSOCIATED OCULAR ABNORMALITIES

Microphthalmos with a small cornea was present in 6 cases. The left eye was microphthalmic in case 2 and also showed remnants of pupillary membrane and a posterior lenticonus; in addition, the left palpebral fissure was narrowed and there was a naevus flammeus of the upper lid and brow on that side. The small left eye in case 4 had remnants of pupillary membrane and a posterior cortical cataract, and the left palpebral fissure was narrower than normal. Both eyes in case 6 were small but exhibited no other discernible congenital defects. Among the cases in which the diagnosis was made at necropsy, there was bilateral microphthalmos in 1 (that of L. M.) and unilateral microphthalmos in 2 (that of B. R. and Jankû's case).

In case 5 there was severe anisometropia. Refractive errors of varying degree were present in all the other cases in this series. Atrophy of

the optic nerve of some degree was observed in many instances. This evidently was secondary to papilledema in case 3 but in the others was atrophy of the primary type due to the destruction of the macula and of other portions of the retina. The intracranial lesions and possibly lesions in the optic nerves also may have contributed to development of the atrophy.

DIAGNOSTIC FEATURES OF TOXOPLASMIC CHORIORETINITIS

Ophthalmoscopically, the intraocular lesions of toxoplasmic encephalomyelitis have certain characteristics that seem to distinguish them clearly and would appear to render them diagnostic. These features may be summarized as follows: (1) occurrence of severe and extensive focal chorioretinal lesions in infants and in children; (2) regularity of bilateral involvement of the macular region; (3) tendency to bilateral occurrence of other lesions; (4) tendency to involvement of the periphery in one or more quadrants of the retina and choroid; (5) punched-out appearance of large and small lesions in the late phase; (6) occurrence of massive chorioretinal degeneration, extensive connective tissue proliferation and heavy pigmentation, as contrasted with the dissociation of these changes in other chorioretinal lesions; (7) presence of an essentially normal retina and vasculature surrounding the lesions in all stages of the infection; (8) tendency to the occurrence of associated congenital defects in the eyes; (9) rapid development of sequential optic nerve atrophy, and (10) constant clarity of the media in the presence of severe chorioretinitis (with one exception, the left eye in case 4).

Diagnostic Significance of Toxoplasmic Chorioretinitis.—Infantile toxoplasmic encephalomyelitis was first suspected in 4 of the 6 cases presented in this report when the characteristic chorioretinitis was observed on routine ophthalmoscopic examination; in the other 2 cases, it was a major diagnostic aid. Subsequent detailed inquiry into the early history, roentgenographic studies of the head, ventriculographic studies, examination of the cerebrospinal fluid and serologic tests established the correct diagnosis in each instance.

Among the cases previously reported in which the diagnosis was not made until necropsy,[5] clinical examinations of the fundi had been carried out in 6 and lesions observed in 5. The presence of intraocular lesions cannot be excluded in 1 case in which such lesions were not observed, since the eyes were not examined post mortem. It would appear that toxoplasmic chorioretinitis occurs in most, if not all, instances of infantile toxoplasmic encephalomyelitis and is of diagnostic aid in the clinical recognition of this disease. It should be regularly sought in infants and children with a history of convulsions, hydrocephalus, mental retardation, speech difficulties, defective vision or intracerebral calcification first observed in early infancy.

DIFFERENTIAL DIAGNOSIS

Toxoplasmic chorioretinitis must be differentiated ophthalmoscopically from (1) pseudoglioma; (2) intraocular tumors, especially retinoblastoma; (3) traumatic lesions, particularly the intraocular sequelae of injury at birth; (4) hereditary cerebromacular degeneration, and (5) congenital developmental defects. The following additional conditions are much less likely to be confused with toxoplasmic chorioretinitis: (6) tuberous sclerosis; (7) acute metastatic chorioretinitis associated with severe infection of the upper respiratory tract; the acute exanthems and certain protozoan diseases, such as malaria; (8) meningitis, particularly the tuberculous form, and (9) granulomas, especially the syphilitic (congenital), tuberculous and leprous types.

Pseudoglioma.—This is a descriptive term employed to include various conditions that may simulate new growths in ophthalmoscopic appearance. Although the etiologic basis remains speculative, pseudoglioma probably results from a previous chorioretinitis. Since it usually exhibits connective tissue proliferation, it is difficult to distinguish from old chorioretinitis, particularly if there are accompanyng signs of inflammation or pigmentation. It is difficult to differentiate this condition from toxoplasmic chorioretinitis, but pseudoglioma usually is unilateral and single, although it does tend to be macular in location. It is necessary, therefore, to consider the other clinical features of toxoplasmosis in arriving at a diagnosis. It is not unreasonable to assume that some cases in which the diagnosis now would be pseudoglioma may prove to be instances of toxoplasmic chorioretinitis.

Intraocular Tumors.—Retinoblastomas usually escape notice until growth results in a yellowish reflex at the pupil. Elevated intraocular tension may be confirmatory, and roentgenographic demonstration of some islets of calcification in the lesion is frequently possible (Pfeiffer [12]). Ophthalmoscopically, gliomas progress from small round yellowish white nodules in the retina to large polypoid masses protruding into the vitreous. Pigmentation and atrophy occur only infrequently and then only to a moderate degree. Bilaterality is the rule.

Hemangioblastomas, melanoepitheliomas and metastatic neoplasms, as well as the so-called "phakamotoses," for the most part do not manifest themselves until the later years.

Traumatic Sequelae.—Abnormalities of labor may result in such intraocular injuries as commotio retinae and in extensive hemorrhages into the retina and vitreous with subsequent scarring of varying degree.[13]

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12. Pfeiffer, R. L.: Roentgenographic Diagnosis of Retinoblastoma, Arch. Ophth. **15**:811-821 (May) 1936.

13. McKeown, H. S.: Retinal Hemorrhages in the Newborn, Arch. Ophth. **26**:25-37 (July) 1941.

The essential differential points between such scars and the lesions of toxoplasmosis are those of pseudoglioma.

Cerebromacular Degeneration.—Ophthalmoscopically, a central brownish to cherry red spot with a marginal whitish band is characteristic of Tay-Sachs disease (infantile form of amaurotic family idiocy); however, the macular area may present nothing more than slight to moderate thickening centrally associated with group pigmentation of some or all of the near and distant retinal periphery. Although the combined occurrence of cerebral symptoms and intraocular lesions is common to this condition and to toxoplasmosis, the opthalmoscopic observations described briefly heretofore do not appear in toxoplasmic chorioretinitis.

Congenital Developmental Defects.—Colobomas of the choroid, the optic disk, the retina and the macula exhibit no evidence of present or past inflammatory activity and typically do not occur in the upper half of the fundus. Thus, they are easily distinguishable from the chorioretinal lesions of toxoplasmosis.

Tuberous Sclerosis.—This is rare in infants and in children. Characteristic single or multiple tumor-like nodules appear at or near the disk and in the posterior third of the retina. These consist of white striated glistening elevated proliferated glial tissue through and over the surface of which there are numerous small highly refractile whitish yellow spheres. The combination of cerebral and ocular lesions necessitates the differentiation of this entity from toxoplasmosis, but the ocular lesions are so different in the two diseases that there should be no confusion.

Acute Metastatic Chorioretinitis.—The chorioretinitis which occurs occasionally in the course of severe infections of the respiratory tract, in association with the acute exanthems, particularly variola, vaccinia and measles, and in the protozoan diseases, such as malaria, probably is the least likely to be confused with that of toxoplasmic chorioretinitis, since the lesions in these diseases occur after the infection has been well established. The lesions tend to occur rapidly and metastatically; they are small and are irregularly but widely distributed throughout the fundus, and frequently generalized uveal infection ensues.

Granulomas.—Ocular syphilis in infancy and in childhood is usually congenital. The characteristic lesions encountered in the fundi are typically diffuse and rather regular in distribution, the many small involved areas occupying most of the visible segments. The tuberculous choroidal foci that occur in the terminal stages of a miliary dissemination of tuberculosis are readily distinguishable from toxoplasmic lesions, since the former are small dull yellow focal areas distributed irregularly

in the choroid. The chorioretinitis of leprosy definitely originates in the choroid, and, as in toxoplasmosis, it may be bilateral and multiple, but the lesions vary in size and in age, occur only infrequently and when they do involve the macular area; bilaterality is unusual.

Differentiation.—The clinical symptoms and signs permit differentiation of toxoplasmic chorioretinitis from the other conditions mentioned when the ophthalmoscopic observations are not clearly diagnostic. Symptoms and signs beginning at birth or early in life, a subacute or chronic course, evidence of widespread involvement of the nervous system, convulsive seizures, internal hydrocephalus and the occurrence of intracerebral calcification all point to the presence of infantile toxoplasmic encephalomyelitis, of which toxoplasmic chorioretinitis is an outstanding feature. Antitoxoplasmic activity of the serum tends to confirm this diagnosis.

SUMMARY

1. The ophthalmologic findings in the first 6 cases of infantile toxoplasmic encephalomyelitis clinically diagnosed are presented.

2. The essential lesion is a toxoplasmic chorioretinitis which is focal, bilateral and frequently multiple. The macular region in each eye almost invariably is involved, but more peripheral lesions often occur. The remaining portion of the retina and the vasculature are normal. The evolution of the lesions is outlined.

3. Toxoplasmic chorioretinitis is an important diagnostic feature of infantile toxoplasmic encephalomyelitis and first led to the suspicion of the presence of that disease in 4 of the 6 clinical cases presented. The differential diagnosis of the chorioretinal lesions is discussed.

4. The pathologic observations in toxoplasmic chorioretinitis are described. These are necrotizing and inflammatory lesions in the retina and in the choroid similar to those found in the brain.

5. The fetal inception of toxoplasmic chorioretinitis is discussed, and the occurrence of associated congenital ocular abnormalities is recorded.

MEDICAL CONSIDERATIONS OF SOME GERIATRIC PROBLEMS

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It is no mere accident that during the past decade increasing attention has been paid to the aging process in its varying aspects. The interest is due to two definite factors that have been exerting a far reaching influence on the nation for many years. They are, first, the noteworthy increase in life expectancy that has occurred and, second, the changing trend in the age composition of the population.

It is unnecessary to dwell at length on the frequently quoted statistics that show the steady increase in life expectancy from antiquity to the present. It is sufficient to emphasize that, whereas from the outbreak of the Revolutionary War until the turn of the nineteenth century, expectancy of life in this country increased only from thirty-five and one-half to fifty years, since 1900 it has shown an increase little short of dramatic. In 1930 the expectancy for the white population was 60 years; at the present time it is between three and four years longer. It has been conservatively estimated that if the present rate of increase is maintained, in another fifteen years life expectancy will reach 75 years. From the medical standpoint the second factor, the shift in the age composition of the population, is probably the more significant. During the past century the percentage of older people in the population has increased. At the same time, the younger element, those 20 years of age or under, has shown a pronounced decrease. In 1850, 52.5 per cent of the total population of the country was under 20 years of age. From then until the present time the percentage has steadily fallen with each decade. By 1900 it had fallen to 44.4 per cent. It has been estimated that at present the percentage is about 35. In the meantime the percentage of persons aged 45 years or older has been steadily increasing. This group comprised 17 per cent of the total population of the United States at the beginning of this century. By 1940 the percentage had risen to 26.5. By projection based on the last census, it is estimated that in 1980 more than 40 per cent of the population will be 45 years of age or over.[1] A hundred years ago persons aged 65 years or over

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1. United States Life Tables (Preliminary): Estimated Future Population by Age and Sex, 1945-1980, Bureau of the Census, United States Department of Commerce, 1941.

represented only about 2.6 per cent of the total population. Today this group comprises about 6 per cent of the population. According to the last census, although the total population of the United States had increased 7.2 per cent during the decade between 1930 and 1940, the number of persons aged 65 or over had increased 35 per cent. On this basis it is estimated that today there are in the United States approximately 9,000,000 persons aged 65 years or older. From these data it is evident that the nation is rapidly becoming a nation of old people, a fact which has implications of far reaching significance not only medically but sociologically, economically and even politically.

In a consideration of the forces that have brought about this unprecedented shift in the age structure of the population, it is apparent that medicine has played a leading role. It is true that the steadily declining birth rate has played a part. This rate has fallen from 30 per thousand in 1900 to about 16 per thousand. Restriction of immigration during the last half century is undoubtedly an added factor, and in the immediate future the devastation of the youth of the country in the present worldwide conflict is destined to accentuate further the relative increase of old people in the population.

It is significant that the spectacular increase in life expectancy has been coincident with the achievements of preventive medicine. As examples of the latter may be mentioned the accomplishments of pediatrics in lessening infant mortality and in controlling the infectious diseases and the nutritional disorders of childhood, accomplishments which have resulted in a striking decrease in mortality during the first ten years of life. Of equal importance are the contributions to health that have resulted from the control of many other infectious diseases and the virtual elimination of disastrous epidemics. To these factors may be added the extensive public health programs that have brought about improved sanitation, better housing, more sanitary working conditions and an awakening of the public consciousness to matters of diet, nutrition, fatigue and personal hygiene. Thus it is that medicine is largely responsible for the years that have been added to life and the startling increase in the number of old people that has resulted. The unprecedented situation which medical science has created now presents problems which must look to medicine for their solution. It is both the obligation and the responsibility of medicine to see that the ever increasing group of older people in the population, whose longevity scientific advance has made possible, are given an opportunity to enjoy their added years in good health, contentment and happiness. The duty of the medical profession toward the aging population of the country has been summed up as follows: "The Society which fosters research to save human life cannot escape responsibility for the life thus extended.

It is for Science not only to add years to life, but more important, to add life to years."[2]

Preventive medicine, by saving life among the young, has increased the number of old people who ultimately become the victims of degenerative disease. The resultant changing trend in the incidence of disease is well shown by a study of the principle causes of death in this country during the last fifty years. It was emphasized by Christian[3] in a discussion of the limitations of preventive medicine when he pointed out that the diseases that play a major part in bringing about the death of the old in general belong to the group of nonpreventable diseases. During the last half century the death rate for preventable diseases, notably the acute infections, has undergone a pronounced decline, whereas that for the various degenerative diseases has steadily risen. Heart disease, which in 1900 was fourth as the causes of death, now holds first place; cancer, which at the turn of the century was ninth, is now second; diabetes mellitus has risen from nineteeth to tenth place; tuberculosis, which less than fifty years ago ranked first as a cause of death, has dropped to sixth place; diarrheal diseases and the various infectious diseases of childhood, which once took such a toll, are now far down in the tables of the causes of death. Until about five years ago pneumonia had remained practically fixed in third place, which it had occupied in 1900. The advent of the sulfonamide compounds happily has so altered the situation that in the last year, in the state of Pennsylvania, for instance, the mortality for this disease has been reduced from about 25 per cent to 7 per cent. These examples are sufficient to indicate the decline in the mortality from preventable diseases during recent years. There has been no such change in the death rate from degenerative diseases. As the number of older people has steadily increased, the incidence of these diseases has become greater. The obvious inference is that more persons are now enabled to live to the age at which chronic disease is prevalent. In short, youth has been conserved, finally to become the victim of degenerative conditions.

The increasing incidence of degenerative diseases in the aging population is destined to have a distinct influence on medical practice. As medical science controls more and more preventable diseases, the at present nonpreventable degenerative conditions will attain greater prominence. In the past the chief medical concern has been with the care and protection of the young. It now becomes incumbent on the physician to meet adequately the growing medical demands of the older population. To do so it is necessary for him to develop a more lively interest in and a better understanding of the problems of old age and

2. Piersol, G. M., and Bortz, E. L.: Ann. Int. Med. **12**:964, 1939.

3. Christian, H. A.: Ann. Int. Med. **12**:1499, 1939.

to become more familiar with its altered physiology and its pathology. A start along these lines should be made in the medical schools. Just as pediatrics is emphasized, so geriatrics should be accorded recognition commensurate with its ever growing importance. The student should early learn that no inconsiderable part of the practice of medicine in the future must be concerned with the degenerative diseases of later life, a proper understanding of which is not only essential to physicians' success but is necessary if they are to fulfil adequately their obligations to the community. Heretofore, the physician has somewhat lacked interest in disease as it appears in the older person, looking on it as irremediable and inevitable. If the medical problems of old age are to be successfully met, he must abandon his defeatist attitude and approach the management of such problems in a spirit of greater constructiveness and optimism. It will then be possible for him to do much to prolong life, relieve suffering and mitigate in no small degree the handicaps and infirmities of old age.

Longevity marred by an accompaniment of disabling disease and suffering has little to commend it; it is a distinct liability rather than an asset. To prevent the development of such an accompaniment is one of the most important and serious responsibilities of medicine. A healthful and useful old age depends on the preventing, or at least the delaying, of the development of those conditions which become disabling during senescence. This point was well stressed by Stieglitz [4] in his plea for preventive geriatrics. He pointed out that the most important diseases of senescence, such as cardiovascular-renal disease, arthritis, diabetes mellitus and cancer, are best controlled in the two decades preceding old age, which students of gerontology agree begins at 60. It is definitely the problem of prophylactic geriatrics to see that those persons who have been conserved enjoy the fruits of their old age. The geriatrician must ever bear in mind that, unlike the pediatrician, who is concerned with young, resilient organisms, in whom disease is usually acute, self limiting and of exogenous causation he is confronted with degenerative processes that are essentially chronic, insidious and of unknown causation in persons with low resistance and of low recuperative power. As Stieglitz stated, the disorders of the latter decades of life are not amenable to mass prevention; they are progressive and essentially individualized, and in the present state of knowledge cure is virtually impossible and control and retardation the best that can be hoped for.

If the physician is to meet his obligations to the aged, he must constantly bear in mind the importance of controlling those presenile states which if allowed to go unheeded will lead to chronic visceral disease,

4. Stieglitz, E. J.: New England J. Med. **225**:247, 1941.

for which little can be done. Among the disorders of this kind metabolic disturbances are prominent, obesity and diabetes being the most important. The obese person is a poor risk, and as age advances he is more susceptible to various cardiovascular and renal defects, as well as to diabetes and disturbances of the gastrointestinal tract, than the person of normal weight. Much can be done by proper dietetic restriction to correct obesity and thereby prevent subsequent disabling disease. The rapid increase of diabetes in the United States makes this disorder of particular importance. The many degenerative changes, notably those of the vascular system, which occur in the neglected aged, diabetic patient emphasize the necessity of bringing this disease under control. The well regulated diabetic patient approaches old age with the assurance that a reasonable degree of good health may be enjoyed and disastrous vascular consequences minimized.

There is steadily increasing evidence that diet plays an important part in human longevity and in delaying or preventing some of the disorders common to senescence. Sherman [5] said that if old persons live on a suitable diet, especially one rich in fruits, vegetables (particularly of the green and yellow varieties), milk and milk products, the expectancy of effective human life may be extended by at least 10 per cent. The same general thought has been advanced by Minot.[6] More recently McCay,[7] basing his observations on a series of carefully carried out experiments on rats, concluded that diet exercises a profound influence on the length of life. Part of this influence, he stated, is due to modification of the chronic diseases that become important in the latter half of life. The weight of clinical and experimental evidence indicates that a well balanced, optimal diet, rich in vitamins, during early adult life, can do much to delay the onset of senility and keep the aged person in a state of health and vigor.

In no field can prophylactic geriatrics be more effective than in the control of vascular degeneration, since the majority of the infirmities of old age depend directly or indirectly on vascular changes. Efforts in this direction are seriously handicapped because of a lack of accurate knowledge as to the cause of arteriosclerosis. In recent years much painstaking study has been devoted to what might be termed the presclerotic state in an effort to prevent the development of severe vascular degeneration. Particular interest has centered on the control of persistent hypertension. It should be pointed out that hypertension and arteriosclerosis are in no sense synonymous. Nevertheless, it must be admitted that long-continued elevation of the blood pressure ultimately brings about vascular changes due to the strain to which the arterial

5. Sherman, H. C.: Bull. New York Acad. Med. **13**:311, 1937.
6. Minot, G. R.: New England J. Med. **215**:1147, 1936.
7. McCay, C. M.: Tr. & Stud. Coll. Physicians Philadelphia **10**:1, 1942.

walls have been subjected. This sequence is seen particularly in diffuse hyperplastic arteriolar disease. If the devastating effects of hypertension on the heart, the central nervous system and the kidneys which are prone to occur as age advances are to be avoided, the persistent hypertension encountered with increasing frequency during youth and early adult life must not be lightly regarded, and in every case serious effort must be made to bring it under control. Without entering into a discussion of the controversial problem of hypertension, it may be stated with little fear of contradiction that up to this time, in spite of the best efforts of physicians, the management of that form of hypertension which is presumably the result of arteriolar spasm, a condition commonly referred to as essential hypertension, has been decidedly unsatisfactory. Therefore, it is particularly heartening to note the stimulating and suggestive work now being done in an effort to solve the riddle of hypertension. In this connection must be mentioned the observations of Goldblatt on the production of renal ischemia by clamping of the renal artery in dogs and in monkeys, with resultant production of hypertension similar to that found in man. Goldblatt found this hypertension definitely lowered by the subsequent removal of a kidney in which the renal artery had been constricted. Further encouragement may be derived from the most recent work of Paige, Cochran and their associates, as well as from that of Harrison, Grollman and Williams, on the presence of a true humeral vasoconstrictor substance and of antipressor substances in the body. Although it is premature to attempt to evaluate the practical results of these experiments, it is certain that they are bringing nearer a solution of one of the most important problems of geriatrics, the cause and control of hypertension.

Although cancer may occur at any age, it is encountered most often in later life, and its increasing frequency constitutes one of the great menaces of old age. Not infrequently cancer has its inception in one of the precancerous conditions that are observed in early adult life. It is, therefore, the grave responsibility of those who seek to practice preventive medicine to keep before them constantly the importance of searching out all conditions that are potentially malignant or that may predispose to the development of cancer in later years. Numerous other examples might be cited of conditions which should be recognized and controlled in an effort to prevent the development of the distressing handicaps of old age, but mention of those referred to, which are the most important, should suffice to stress the fact that the constant endeavor must be to treat the aging rather than the aged. This endeavor is the major role of geriatric prophylaxis.

There are few if any diseases that can properly be designated as peculiar to, and restricted to, old age. Practically all disease conditions observed in the aged are also encountered in younger persons, and,

conversely, there are few if any diseases that may not at times be found in old people. The only exception to this statement are certain changes which occur with such frequency in the old and are so devoid of symptoms that they can hardly be regarded as diseases and may be looked on as physiologic in the aged. In this category fall such changes as graying of the hair, the arcus senilis, the atrophy which takes place in all lymphoid tissues, the senile type of emphysema with its attendant decrease in vital capacity, the osteoporosis of the long bones and the larger flat bones, the atrophy of the intervertebral disks with its resulting loss of height and lowering of the vertebral column, the decrease in the capillary beds of the skin giving rise to the pallor so frequently mistaken for anemia and the general decrease in or absence of the deep tendon reflexes, as well as the atrophy observed in the thyroid gland, liver, spleen, kidneys and other organs, with the notable exception of the heart, which frequently maintains its normal relation to the total body weight. As Pepper [8] has pointed out, "These physiological changes form a base line which should be looked upon as normal for individuals of older age even though they deviate remarkably from what is accepted as normal in younger aged groups."

Since with the possible exception of the changes cited, there are no diseases due to old age per se, geriatrics is in reality the study of all disease conditions as they manifest themselves in the aged. The great problems in geriatics are the way in which structure and function are altered by old age and the special way in which old persons react to various stimuli. Only through study of these problems will it be possible to determine what is to be regarded as within the limits of normal for the aging organism. A reaction which could be regarded as highly pathologic in a young adult may well be of no significance in a person who is senescent. For example, it is a recognized fact that older persons get along with much less sleep without detriment than do those who are younger. What might be regarded as insomnia of pathologic significance in a person of 20 might well be within the normal physiologic limits of one who is three score years and ten. Because of altered physiology and special reactions, disease has manifestations in old persons quite different from those encountered in younger ones. These modifications must be clearly understood and appreciated if symptoms in the aged are to be properly evaluated and interpreted.

In the diagnosis of diseases of old age, ophthalmology has made important contributions. In no other field are these so evident as in the all-important diseases of the vascular structures, which are so largely responsible for most of the pathologic conditions encountered in older persons. The ophthalmologist is often responsible for the recognition of

8. Pepper, O. H. P.: M. Clin. North America **20**:1, 1936.

arteriosclerotic changes, having observed them in the retinal vessels long before they could be noted elsewhere. Chief dependence must be placed on examination of the eyegrounds for the early recognition of hypertension and for the differentiation between that due primarily to vascular disease and that due to vascular changes resulting from an underlying renal condition. It is unnecessary to dwell on the importance that attaches to the recognition of retinal hemorrhages and exudates, papilledema, opacities of the vitreous, alterations in the tension of the eyeball and changes in the crystalline lens, not to mention altered pupillary reactions and palsies of the extraocular muscles, in the early recognition and diagnosis of many of the diseases frequently encountered in old persons. The importance of ophthalmoscopy as a diagnostic procedure is so well recognized that today examination of the eyegrounds is a part of the training of the internist and the ophthalmoscope is as essential a part of his diagnostic armamentarium as the stethoscope or the sphygmomanometer.

It would be as impractical for me to attempt to discuss in detail the treatment of the various diseases that afflict the aged as it would be for me to undertake a systematic consideration of the clinical manifestations of these disorders. Nevertheless, since the management of disease in the aged has attained such prominence, it is time attention was directed to certain broad principles of therapy based on the altered physiology and psychology of the senescent. There are many persons who have never learned to accept their advancing years philosophically. Such persons bitterly resent being told that their infirmities are due to old age and must be borne with equanimity. Whether the practitioner feels it or not, a spirit of optimism and hope should be brought to the bedside of the aged patient. Although cure is impossible and improvement is the best that can be hoped for, such a patient is entitled to the best efforts of the physician and must be handled with infinite patience, tolerance, gentleness and sympathetic understanding. The therapeutic rules applicable to young persons must be modified when one is dealing with those who are older. Old people react badly to sudden change. They do better in the environment to which they have been long accustomed. Even the presence of strangers may disturb their psychologic equilibrium. Transfer to the unaccustomed surroundings of a hospital may produce unfortunate psychic results, a fact only too well known to many ophthalmologists, who find it necessary to hospitalize old persons for such procedures as cataract extraction. Prolonged rest in bed is frequently detrimental to the aged, especially those in whom myocardial degeneration exists. The enforced inactivity and maintenance of the recumbent position are important contributory factors to pulmonary congestion and often lead to bronchopneumonia. This is true not only

in ophthalmologic cases but, more especially, in cases of fracture of the neck of the femur or of prostatectomy, in which the wise rule is to get the patient out of bed at the earliest possible time.

An excellent example of the importance of appreciating what is to be regarded as physiologically normal for an older person is the disastrous result which often follows a determined effort to bring an elderly patient suffering from a chronic disease back to a level that is normal for a younger person. The danger of such a result should be impressed on the overenthusiastic younger clinician. A lesson is furnished by the institution of radical measures in an attempt to bring down the blood pressure to a so-called normal level in a patient who, over a period of years, has apparently become adapted to a pronounced hypertension. Diabetes furnishes another excellent example. Many an aged diabetic patient who has lived comfortably in a state of equilibrium with a blood sugar level far in excess of normal is suddenly thrown into cardiac failure or cerebral or coronary thrombosis as a result of drastic efforts to bring the blood sugar level down to normal and to keep it there. Radical alterations in diet are frequently resented and badly borne by older persons, who, having attained a ripe and comfortable old age on a diet seemingly ill balanced and bizarre, are reluctant to abandon the habits of a lifetime to adopt a plan which, though theoretically perfect, may be both distasteful and disturbing to them. It is a well recognized fact that old people bear drug therapy badly, especially the use of opiates and hypnotics, which when administered should be given cautiously and in small doses. The defective elimination in old people makes them more liable to the cumulative action of certain drugs, particularly some of the sedatives, and it is not unusual to observe a temporary but severe psychosis from the persistent use of even small doses of the barbiturates. In short, in the management of the aged every effort should be made to disturb as little as possible the habits of life which have become firmly established over many years. Procedures which subject the patient to sudden psychic and physical shocks are apt to be productive of more harm than good and should be carefully avoided.

It is natural that the chief interest of the physician should center about the clinical aspects of gerontology. Nevertheless, as a public spirited citizen playing an active part in a world in which the social and the economic order are rapidly and inevitably changing, he must not be unmindful of some of the broad sociologic problems which the changing age composition of the population is forcing on the nation. Improved medical care and a better understanding of the physiology of aging will do much to lessen the sufferings of the aged and to mitigate to some extent the unhappiness experienced by many of them. These results, however, are not enough if the physician is to meet the responsibilities

placed on him by the presence of the aged. Not only the medical but the social aspects of the problem must be solved. It is not so much death that is feared by old people as the dread of idleness, of uselessness after a life of activity and of loss of economic independence. Means must be found to educate people to plan for their later years. Their planning must involve more than an effort to accumulate enough money to sustain them in old age, although it is true that the assurance of economic security adds in no small degree to the peace of mind of those approaching senescence. This fact is well recognized and has been given concrete expression in the social security and old age pension acts that have been instituted by the Federal Government and by many states. Although the pensions provided will to some extent meet the needs of the poor, they are obviously inadequate to allow most older persons to live at the social and economic level to which they have become accustomed and on which their contentment depends to a considerable degree.

There is a tendency to expect old people to accept compulsory retirement along with the dole. Such a scheme is both unfortunate and unsound sociologically and psychologically. The best insurance against unhappiness in old age is to be found in occupation. It is clearly the duty of society to educate older persons to help themselves. The problem of providing useful occupations for this ever increasing group should be given careful study. They should not be asked to compete with youth or to labor with the same intensity that characterized their more active period of life. The present appalling situation, with its wanton destruction of youth and the diversion of large numbers of young workers from productive occupations, is destined to provide many examples of effective ways in which the older element of the population can, when necessity arises, be occupied to advantage.

This aspect of growing old was well summed up by Cowdry,[9] when he stated:

> The most effective preparation for advanced years is the cultivation of some line of activity which can be carried on as we become more and more physically feeble. The really happy aged person holds his head high, consequently avoids a feeling of inadequacy, because he or she is able to do something extremely well. It makes little difference what this something is so long as its value is appreciated by others.

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9. Cowdry, E. V.: Scient. Monthly **50**:51-58, 1940.

FIBROBLASTIC OVERGROWTH OF PERSISTENT TUNICA VASCULOSA LENTIS IN PREMATURE INFANTS

II. REPORT OF CASES—CLINICAL ASPECTS

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So-called persistent tunica vasculosa lentis, or a fibroblastic sheath behind the crystalline lens, is known to occur sporadically. Usually the condition is discovered a few days after birth in an infant born at full term, but the correct diagnosis is often not established until the eyes are examined pathologically after removal because of a clinical diagnosis of retinoblastoma. Almost invariably this lesion is unilateral. That it is infrequent is borne out by the paucity of the literature on the subject and the scarcity of pathologic specimens.[1]

Within the last year a similar condition has been found in both eyes of a number of infants born about eight weeks prematurely. This bilateral fibroplasia [2] at first appeared to be a new disease entity related to prematurity. Only after study of cases 5 and 7, reported hereafter, was it apparent that the condition observed sporadically at birth was a different phase of the disease seen in the prematurely born infants. The lesion in premature infants evidently develops after birth, since in

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This study was made possible through a special fund for research for the Pathology Laboratory of the Massachusetts Eye and Ear Infirmary.

1. (*a*) Fleming, P., and Parsons, J. H.: Tr. Ophth. Soc. U. Kingdom **23**: 242, 1903. (*b*) Collins, E. T.: Developmental Deformities of the Crystalline Lens, J. A. M. A. **51**:1051 (Sept. 26) 1908; Tr. Sect. Ophth., A. M. A., 1908, p. 452. (*c*) Howard, H.: Tr. Am. Ophth. Soc. **15**:244, 1917. (*d*) Lane, F.: Arch. Ophth. **48**:572, 1919. (*e*) Lent, E. J., and Lyon, M. B.: Am. J. Ophth. **5**:706, 1922.

2. Considerable thought has been given to the selection of an appropriate term for this disease condition. Early in the study, when the condition was thought to be represented fully by a massive growth of embryonic connective tissue behind the lens, the term "retrolental fibroplasia" was formulated by Dr. Harry K. Messenger. As the study progressed, it was proved that many other conditions also belonged to the disease entity, but so far no all-inclusive name has been devised. Perhaps the term "fibroplasia" might be as satisfactory as any, because all the changes appear to be related to a mesodermal overgrowth or to a persistence of embryonic mesodermal tissue, and so far as I know this term has not been used for any other condition.

no case was it noted before the age of 4 months. The apparent frequency of this bilateral condition in infants born prematurely is impressive. In less than one year I have observed it in 7 infants, it has been known to exist in 8 others and it probably was the pathologic change in 5 more.

These infants have shown changes based in some degree on the following three principles:

1. Persistence of all or some part of the hyaloid vascular system. The remains may be in the form of either vessels carrying blood or parts of closed blood vessel walls.

2. The presence of embryonic connective tissue growth behind the crystalline lens.

3. Persistence of the fetal character of the vitreous humor, i. e., a fibrillar structure.

The specific findings may include the following ones:

1. Persistent pupillary membrane. (This can arise independently.)

2. Congenital crowfoot pigment on the crystalline lens.[3] (This can arise independently.)

3. Congenital posterior synechia through failure of the connection between the tunica vasculosa lentis and the iris mesoderm to disappear.[3]

4. Persistent tunica vasculosa lentis.

5. Persistent hyaloid artery.

6. Retrolental fibroplasia.

7. A type of congenital cataract.

8. Mittendorf dot.

9. Pseudopapilledema with hypermetropia because transparent unyielding remains of hyaloid artery with ocular growth prevent the papilla from receding or even cause the optic nerve fibers to be pulled into the globe.

10. Glial projections and congenital retinal folds resulting from traction, as the eye enlarges, of unyielding fibrils of vitreous.

11. Shallow anterior chamber.

12. Microlentia.

13. Microcornea.

14. Microphthalmos.

REPORT OF CASES

CASE 1.—E. B.,[4] a boy 6 months old, was referred for examination of the eyes because the parents and the pediatrician felt that he had some visual defect. The fundus could not be seen because of a grayish opacity in the pupillary area of

3. Terry, T. L.: Tr. A. Research Ophth., 1942, to be published.

4. Terry, T. L.: Am. J. Ophth. **25**:203, 1942.

each eye. The general color of the opacity was that of a relatively mature cataract. The anterior chambers were extremely shallow. The pupils reacted to light, and the eyes could be transilluminated normally, a yellowish red color being seen in the pupillary area when a small, strong, shielded light was applied to the sclera. The examination was unsatisfactory not only because of the uncooperation of the patient but because of an almost constant irregular searching movement of the eyes. The absence of any discernible iris shadow on the opaque membrane led to the erroneous conclusion that bilateral congenital cataracts were present. The iris shadow was not seen because of the diminutive pupil and the distance between the iris and the opacity. Because of repeated difficulty experienced in attempting to dilate the pupils of young infants, perhaps because of the slowness of postnatal differentiation of the dilatator pupillae muscle, no attempt was made to obtain mydriasis at the first examination. The presence of a pupillary response showed that a functioning retina was present in each eye, and the clear transillumination was additional evidence that no neoplasm was present. However, when the infant was hospitalized for an examination under ether and for discission of the cataracts, the full extent of the diagnostic error was manifest. When mydriasis was attempted the night of admission, it was evident that the opacity was not immediately behind the iris. Because of the original conclusion that the lesion represented more or less total opacity of the lens, it was considered perhaps a subluxation of the lens, since movements of the eye seemed to shift its depth and location. Dr. S. H. Clifford, the pediatrician, agreed to await full mydriasis and a detailed examination with the infant under ether anesthesia before altering the plans for some type of operation. However, the following morning the true nature of the lesions was evident when blood vessels were discovered in the membranes by Dr. P. A. Chandler. Only the day before Dr. Clifford and Dr. Chandler had consulted Dr. F. H. Verhoeff about the eyes of another infant born prematurely, and Verhoeff in that case had arrived at a diagnosis of bilateral persistent tunica vasculosa lentis. Verhoeff confirmed the diagnosis in my case also. The evidence consisted in small eyes, shallow anterior chambers and grayish vascularized tissue immediately behind the crystalline lenses. At the extreme periphery, dentate processes, corresponding perhaps to attachments to ciliary processes, were evident. Between these processes a red fundus reflex could be seen.

The following antepartum history was obtained from the obstetrician and the pediatrician:

The mother had had two previous pregnancies. The first was entirely normal, although the placenta was retained. The child from this pregnancy is now a normal boy. At her second pregnancy the mother was delivered of a stillborn infant three weeks past term.

During the third pregnancy the presence of twins was diagnosed at twenty-three weeks. The patient was under treatment for bacilluria, discovered five weeks previously. The membranes ruptured at seven and one-half months. Four days later the mother's temperature rose to 102 F. Termination of pregnancy was started by administration of 2 minims (0.12 cc.) of solution of posterior pituitary. Soon after, the temperature rose to 105 F., and the dose was repeated, so that 4 minims (0.24 cc.) had been given. The first twin (patient 1) was delivered spontaneously and the second twin about an hour later.

Two days after delivery the mother had a sudden chill and the temperature rose to 107.8 F. Cultures of material from her uterus showed enterococci (streptococci) and gram-positive spores that were not gas producing. Cultures of the urine showed enterococci (streptococci). Therapy with sulfanilamide, later changed

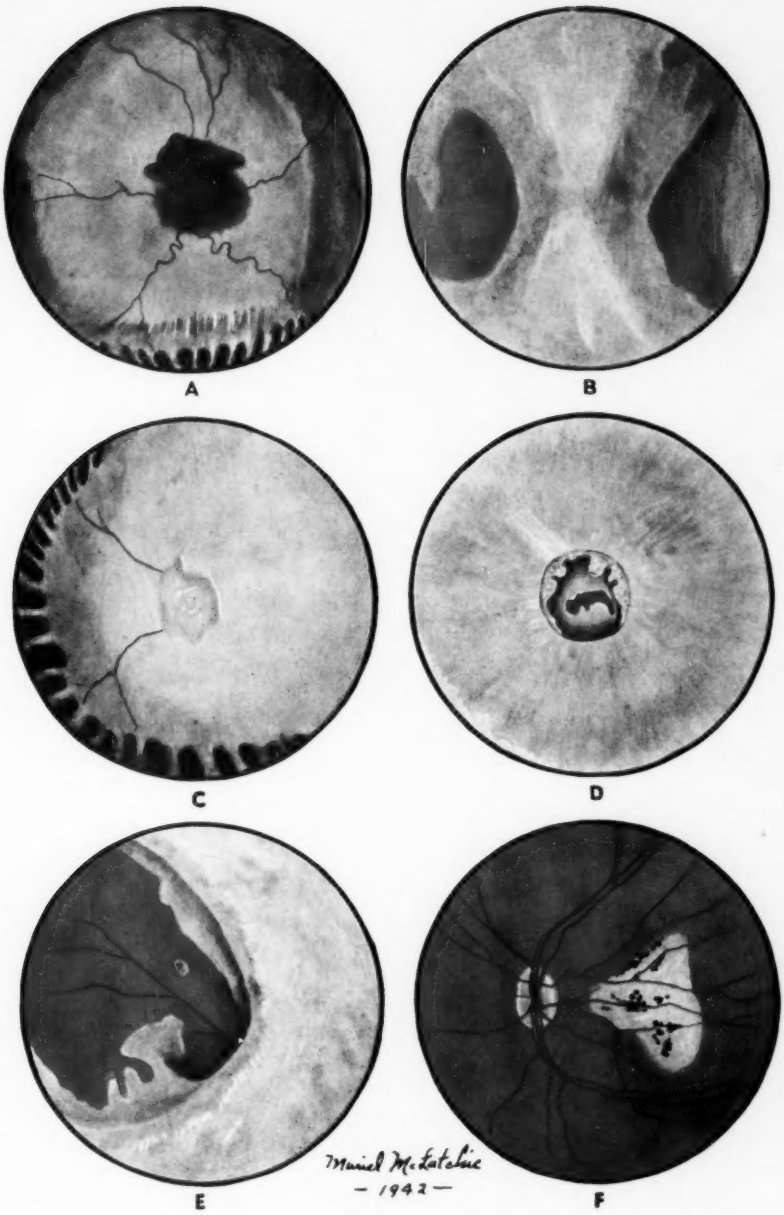

Fig. 1.—Ophthalmoscopic appearance of fibroplasia. *A* (case 1; age, 9 months): Dentate processes apparently correspond to ciliary processes and must represent adhesions. They can be seen at the extreme periphery in all directions. The size of the vessels is exaggerated. *B* (case 1; age, 21 months): The membrane is undergoing lysis or has stretched and torn with the growth of the eye. *C* (case 2; age, 6 months): There is a dense membrane, with no fundus reflex through the spaces between the dentate processes. *D* (case 3; age, 8 months): Hemorrhage is present in the membrane. There are yellowish pigment at the pupillary margin and a white opacity near the angle of the iris nasally. These changes disappeared in time, but the membrane is still extremely dense. *E* (case 4; age, 19 months): The membrane is incomplete nasally. Strands from it extend to the area of retinal separation. *F* (case 6; age, 7 months): Eye with a normal anterior chamber and no retrolental membrane. The fundus lesion resembles healing chorioretinitis.

UNIV. OF MICH.

to sulfathiazole (2-[paraaminobenzenesulfonamido]-thiazole), was instituted. The infection subsided, and the mother was discharged from the hospital in two weeks.

The pediatrician's notes on the twins were as follows: "The second twin weighed 1,006 Gm. (2 pounds 3½ ounces). This baby showed gasping respirations with marked retraction of the sternum and cyanosis. The lungs were almost completely dull to percussion. The baby died after about twelve hours.

"The first twin (patient 1) weighed 1,021 Gm. (2 pounds 4 ounces). The child was examined at the age of 10 minutes, at which time the respirations were gasping and irregular with slight retraction of the costal margins and moderate cyanosis. The lungs were generally dull, with poor breath sounds and many fine rales. The baby was immediately given oxygen. After about ten hours his condition improved, although he still had considerable atelectasis, especially of the posterior part of the right lung. The muscle tone was good. The temperature was 96 to 98 F. The baby was given oxygen continuously, and the environmental temperature was kept at 90 F. On the second day the baby's temperature was 96.5 F.; the temperature of the bed was 85 F., and the administration of oxygen was continued. He was given a small clysis of saline solution and nothing by mouth. On the third day a second clysis of saline solution was given; the baby was slightly dusky, but otherwise the color was good, as was the cry.

"Two days after birth, gavage feedings were started; the baby's condition was considered good. His course was uneventful until the age of 17 days, when he had two cyanotic attacks. At this time the right side of the chest was found to be dull posteriorly; the left was normal. The next day the weight was still 2 pounds 4 ounces. The physical findings were the same. On the second and third days after this he had two cyanotic attacks. His clinical course was uneventful thereafter.

"At the age of 54 days his length was 16½ inches (42 cm.); at birth it had been 15½ inches (39 cm.). At this time I made a note that his eyes seemed normal; the cornea still seemed a bit milky; the pupils were small and did not react. The lens seemed normal.

"At the age of 76 days he weighed 5 pounds 5 ounces (2,410 Gm.) and was 18 inches (46 cm.) long. At this time I made a specific note that the lens appeared normal and the red reflexes normal.

"When the child was 6 months old, weighing 13 pounds 8 ounces (6,123 Gm.), the first note was made that the red reflex could not be obtained and that an opacity was seen in the lens of each eye."

With the diagnosis of the ocular condition established, what treatment could be offered? Among the possibilities were removal of the lens and the membrane, irradiation, temporizing, use of abundant vitamins and sealing of the hyaloid artery in the vitreous by means of diathermy.

It was decided to temporize in order to determine the proper treatment for the condition. Meanwhile the patient was given massive doses of vitamins. When he was 9 months of age artist's drawings of the eyes were made (fig. 1*A*). When he was 14 months old the searching movements had abated considerably, but at the time of writing they are still slightly evident. Examinations at intervals of four to six weeks have shown that the membrane is thinning, although the left eye has improved more than the right. The child acquired the trait of putting the back of the hand or the index finger against either or both eyes, especially when exposed to bright light (fig. 2). There is no rubbing or pressure applied as if the eyes were irritated. An internal squint of some 10 degrees developed in the left eye in spite of the more evident change in the membrane in this eye. Since the baby was 16 months of age miotics have been used because of the

glaucoma noted in 2 other infants (patients 2 and 3). An area several disk diameters in size in the fundus of the left eye temporal to the macular region showed a whitish color, as if chorioretinitis had been present. Involution of the fibroplasia has continued (fig. 1*B*).

CASE 2.—J. D., a girl of 6 months, was brought to the Sachs service of the Massachusetts Eye and Ear Infirmary because the parents thought she could not see. The infant was one of twins, and the parents had noticed that the other child's eyes had shown a change from baby blue to brown, the color of both parents' eyes. The difference in the eyes of the two babies had first been noted about two months previously.

The anterior chambers were shallow, almost nonexistent. Jerky, nystagmoid movements similar to those in case 1 were noted. The eyes were abnormally small, giving an appearance of enophthalmos. The retrolental membranes were grayish, and small blood vessels were readily seen, as if radiating from a central point. At the periphery serration of the membrane was present in all directions. The peripheral dentate processes appeared to correspond in position and number to

Fig. 2.—Typical position of the hands when the infant is exposed to bright light.

the ciliary processes, as if attached to their tips, as in case 1. Through the spaces peripherally one could not see a red reflex, as in case 1, but a shadow-like darkness seemed to occupy the space. The left eye was more extensively involved than the right (fig. 1*C*).

A detailed record of the antepartum and obstetric care of the mother and of the hospital care of the twins was obtained from the New England Hospital for Women and Children. The pregnancy had been uneventful except for a cold which the mother contracted in the sixth month. This cold was followed by soreness of the left eye with swelling and secretion. The mother was given an ointment containing ammoniated mercury. After use of the ointment the eye became very red, and a V-shaped area of hyperemia appeared on the anterior part of the neck. A diagnosis was made of questionable sensitivity to mercury.

The membranes ruptured at seven months, and six hours later the patient was delivered of twins. The first (patient 2) weighed 1,673 Gm. (3 pounds 11 ounces). The second, now a perfectly normal baby, weighed 1,445 Gm. (3 pounds 3 ounces). Immediately after birth the babies were placed in Hess beds.

Because of a failure to gain weight the first baby was kept in the hospital for five weeks. When she was discharged, it was stated on her record that her eyes showed no abnormality. The second twin was hospitalized for four weeks and at discharge was also pronounced perfectly normal.

In view of the repeated suggestions from colleagues in many medical centers of the possible value of radiation therapy, this treatment was suggested to the parents. They were told that the treatment might have some curative effect through the closure of blood vessels or through a direct effect on the membrane itself, but were given full opportunity to refuse if they so desired. The x-ray department of the Massachusetts General Hospital agreed to administer radiation, and it was decided to treat the left eye only. The first dose was 300 r, the voltage 200 kilovolts, the filter 0.25 mm. of copper and the distance 50 cm. After an interval of three weeks a similar dose was administered. Eight days later the eye showed moderate hyperemia, which subsided in a week. Three weeks after the second treatment the membrane in the left eye had become appreciably thinner in its nasal third, and some color of the fundus reflex could be seen faintly through the membrane. However, this improvement was of short duration, and both eyes showed definitely increased whiteness and loss of transparency in the retrolental membrane. It was thought this might be the development of posterior cortical cataracts until, with the passage of more time, the opacities again thinned appreciably, especially in the right eye.

About fourteen weeks after the second radiation treatment a third dose of 300 r was given to the left eye. The pupils were dilated with atropine sulfate for study, as had been the routine at each visit. Four days later the left eye became red and painful as a result of an attack of acute glaucoma. With the infant under ether anesthesia it was found that the tension in each eye was elevated, being 35 in the right eye and 50 in the left (Schiøtz). A paracentesis was done on the left eye. The opening was made under a flap, as if an iridectomy *ab externo* were to be performed. When the anterior chamber was opened, a small amount of aqueous ran from the eye, and the tension was immediately reduced to well within normal limits, so that the eye felt almost mushy soft to palpation. The glaucoma in the right eye was controlled by miotics. During convalescence a cystoid cicatrix developed under the conjunctival flap, and the patient was readmitted to the hospital two weeks later, at which time the paracentesis was repeated in the left eye.

In two months glaucoma was again evident in the left eye. This was controlled by miotics administered in the hospital after an infection of the middle ear had delayed the surgical intervention that had been planned. The eyes have not become enlarged in spite of the episodes of glaucoma. The infant apparently still sees slightly with each eye, as she turns her head and eyes toward the light.

It must be stressed that the worsening of the two eyes was equally severe, even though only the left eye received the roentgen ray treatment. Glaucoma was also present in each eye, but only the left eye required surgical intervention. The mydriasis, induced for study, may have precipitated the glaucoma, and the severity of the disease in the left eye may be related to radiation hyperemia of the ciliary body. The absence of hydrophthalmos is of interest, as it is not known how much glaucoma is necessary or how long it must be present for an overdistention of the eye to be evident. The fibroplasia and consequent distortion of the ciliary processes, the shallow anterior chamber and perhaps the improper differentiation of the meshwork of the iris angle may make glaucoma in association with retrolental fibroplasia behave differently from the usual congenital glaucoma.

From time to time the twin sister of this patient has been examined. Her vision appears to be normal. Both twins have been examined by the members of the pediatric department of the Massachusetts General Hospital and by Dr. Paul C. White, cardiologist, who found them perfectly normal for their age.

The child with the visual defect seems slightly more advanced than her sister both mentally and physically.

CASE 3.—M. S., a girl 7 months old, was referred to the Massachusetts Eye and Ear Infirmary by Dr. Roscoe Meyers, of Worcester, Mass., who first examined her eyes. The parents had noted that the infant paid no attention to them. There was nothing unusual in the antepartum history except that the mother had "menstruated" at intervals throughout her pregnancy and had contracted bronchitis two weeks before delivery, which occurred three days after the membranes ruptured. Her Kahn test and the Kahn and Hinton tests of cord blood were negative. It was estimated that the child represented a 6 month fetus. She weighed 907 Gm. (2 pounds) at birth but lost 113 Gm. (4 ounces) during the three days following birth. She remained in the hospital for seventy-three days, and at discharge her weight was 2,552 Gm. (5 pounds 10 ounces). No general or ocular defects were noted.

Examination showed that the anterior chambers were extremely shallow. The iris appeared baby blue and undeveloped, and mydriasis could not be obtained in either eye. A typical grayish, vascularized membrane was present behind each crystalline lens. In the membrane in the left eye a comma-shaped area of hemorrhage was present. Some posterior synechias were present, and deposits of uveal pigment were seen on the anterior surface of the lens in each eye. Both eyes could be transilluminated clearly A peculiar xanthochromic, roughened "exudate" was present at the pupillary margin in the left eye, and peripheral opacities deeply placed at the margin of the cornea suggested incomplete formation of the iris angle (fig. 1*D*).

The hemorrhage in the left eye increased from day to day. Although it was doubtful whether any vision was present, it was thought best to attempt to stop the hemorrhage by applying diathermy to the hyaloid artery within the eye. With the infant under light ether anesthesia, a conjunctival flap was made about 7 mm. from the limbus, below the external rectus muscle. The sclera was excised to the choroid, and the opening into the eye was completed with diathermy. A small amount of watery fluid, with the consistency of aqueous, flowed out. The diathermy electrode, 1.5 mm. in diameter, was insulated with vulcanite except for the terminal 3 mm. It was inserted into the globe well past the center of rotation in a direction some 30 degrees below the horizontal. Slight resistance was met with as the instrument was inserted. When it projected some 7 mm. into the eye, the current was turned on, a setting on the Walker instrument of 48, approximately that used for cyclodiathermy, being employed, and the instrument handle was slowly lowered, so that the portion in the eye slowly swept upward across the vitreous. Considerable resistance was met as the anterior chamber deepened temporally and below and as the lower temporal portion of the lens was pulled backward and to the nasal side. This behavior was consistent with the opinion that the diathermy needle, though it may have coagulated the blood in the hyaloid artery, certainly did not sever relatively strong connections between the crystalline lens and the nerve head. The instrument was restored to its original position in the eye, and the maneuver was repeated. This time the pupil was displaced nasally, and the lens retained its abnormal position of nasal subluxation, with the lower, temporal edge displaced backward. The anterior chamber was now of relatively normal depth. The wound was covered by closure of the conjunctival incision.

The lens returned to its normal position, with a recurrence of the shallowness of the anterior chamber and reposition of the pupil, in about four days. Although the operative trauma may have caused the hemorrhage in the membrane to

increase about 30 per cent, as time passed the hemorrhage gradually was absorbed. Three weeks later the pupil dilated somewhat better and the brownish "exudate" at the pupillary margin had disappeared. Six weeks later the mother noted that the baby was rubbing her eyes and that the right eye was red. At this time the right pupil could be dilated much more fully with a mydriatic, and the membrane was thinner temporally. Each eye was soft to palpation. Four months after the application of diathermy to the hyaloid artery the tension was elevated in the left eye and there was evidence of iris bombée even though the anterior chamber was very shallow. An iridectomy *ab externo* was done. The abnormal intraocular pressure has not recurred.

The possibility of persistent foramen ovale or patent ductus arteriosus as an etiologic factor [5] prompted consultation with a cardiologist. Dr. Paul C. White made the following comment: "I believe that there may be present in this baby a congenital cardiac defect consisting of a ventricular septal opening, but I doubt that it is in any way responsible for the ocular condition. I would regard it as simply an associated deformity. A fairly loud systolic murmur is present over the entire precordium and is heard also, although less well, in the back; it is maximal at the left of the lower end of the sternum and is attended by a slight thrill. There is no diastolic murmur or abnormality of heart sounds. The blood pressure is now 80 systolic and 50 diastolic in the right arm and 75 systolic and 60 diastolic in the left leg—essentially normal readings and probably against a diagnosis of coarctation of the aorta. The electrocardiogram is normal; the roentgenogram shows a horizontal full-sized (? slightly enlarged) heart with 'normal' great vessels."

The eyes were examined periodically. When the infant was 19 months old, the whitish appearance at the periphery of the cornea had disappeared. Under mydriasis, the right pupil was pear shaped, but three months later it was again round. At this time neither pupil would dilate satisfactorily with cocaine hydrochloride, epinephrine hydrochloride or eucatropine hydrochloride. At the time of writing the eyes are beginning to take on a brownish tone, similar in color to that of the parents' eyes. Although it is questionable whether this child has any vision, she does blink her eyes when exposed to direct sunlight.

CASE 4.—C. N., a girl 6 months of age, was brought to the Sachs service of the Massachusetts Eye and Ear Infirmary because she rubbed her eyes considerably.[6] Both eyes appeared enophthalmic. They seemed somewhat smaller than normal; the anterior chambers were shallow; the pupils reacted to light, and jerky, uncoordinated ocular movements were present. When the infant was 19 months old, mydriasis was induced and she was put under ether anesthesia, and a grayish white, cotton-like substance was observed behind each crystalline lens. Vessels were present in the membrane. In the left eye the membrane was incomplete nasally and the retinal blood vessels could be seen with a + 8 D. sphere lens. Some strands from the retrolental membrane extended deeply; apparently they were adherent to a small, rounded area of retinal separation. The edge of the membrane at another place seemed folded back slightly (fig. 1*E*).

This picture resembled that in the 3 preceding cases so closely that prematurity was suspected. On questioning of the parents it was learned that the baby had been born eleven weeks prematurely, weighing 1,531 Gm. (3 pounds 6 ounces). In addition to administering large doses of vitamin A and riboflavin to the infant,

5. This will be discussed further in a later publication.

6. The diagnosis of bilateral persistent fibrovascular sheath was made by Dr. E. B. Dunphy four months previous to the date when patient 1 was first seen.

the parents kept her in abnormally warm surroundings, causing her to perspire freely.[7] When the child was 2 years old, some internal strabismus of the right eye had developed, and the left eye had improved.

An examination at the age of 26 months showed continued improvement in the left eye. The membrane was thinning, and in the central area none could be seen. The pupil of the right eye did not dilate temporally. It is possible that the iris was adherent to the cornea as well as to the lens temporally. In this eye a small strand of opaque tissue was seen running from the central third of the cornea on the temporal side into the pupillary area. Along the lower edge, a blood vessel carrying blood could be seen. There was no history of inflammation of or trauma to the eye.

Case 5.—J. F., a 7 month old boy, was referred to the Massachusetts Eye and Ear Infirmary because the parents were certain he could not see. The parents had noticed that he did not focus his attention and was interested only in objects within his reach.

This child was one of twins born about six weeks prematurely. The other twin died after one day, the postmortem diagnosis being intracranial hemorrhage. The antepartum history was essentially noncontributory, the pregnancy having terminated after the membranes ruptured.

The weight at birth was 1,517 Gm. (3 pounds 5½ ounces). Evidence of intracranial hemorrhage was noted, and vitamin K (1.6 mg.) was given. Examination of the blood soon after birth showed a hemoglobin content of 128 per cent, 5,120,000 red cells and 12,000 white cells. The baby's progress was irregular. On the third day the temperature dropped to 90.8 F. A spinal puncture yielded 4 cc. of xanthochromic fluid. Three blood transfusions of 20 cc., 30 cc. and 35 cc., respectively, were given, and therapy with sulfadiazine (2-[paraaminobenzenesulfonamido]-pyrimidine) was started. After two weeks the baby began to improve, and he was discharged at the age of 2 months with a weight of 5 pounds 5 ounces (2,410 Gm.). At the time of discharge no abnormality of the eyes was noted.

Examination of the eyes at the age of 7 months showed bilateral retrolental fibroplasia. The anterior chambers were typically shallow, and the eyes showed the usual jerking, nystagmoid movements. The pupils reacted well, and mydriasis caused complete and regular dilatation. With mydriasis the membrane was found to be the least in amount that had been noted in any case and was largely limited to the periphery. In each eye the hyaloid artery could be seen. Unusual folds in the retina could also be made out. These resembled somewhat the folds depicted by Mann.[8] Since this child has been seen only twice, it is impossible to state whether the membrane is in a process of development or of regression. The eyes are taking on a definitely brownish color, and the anterior chambers have appreciably greater depth.

Case 6.—A. S. L., a boy 7 months of age, was brought to the Goodall service of the Massachusetts Eye and Ear Infirmary because the local physician saw a "spot" in the right eye.

Examination showed in the right eye typical retrolental fibroplasia with blood vessels and a dentate periphery. The anterior chamber was extremely shallow,

7. The low body temperature of the premature infant in the incubator as an etiologic factor will be discussed in a later publication.

8. Mann, I.: Developmental Anomalies of the Eye, London, Cambridge University Press, 1937, p. 223.

the eye was somewhat smaller than normal and the iris markings were characteristic of so-called baby blue indistinctness. The left eye appeared normal in size, in color and in depth of the anterior chamber, but occupying the macular region of the fundus was a somewhat triangular, slightly elevated, whitish area mottled in places with increased pigmentation. The general picture resembled chorioretinitis that is beginning to heal (fig. 1*F*).

The question of prematurity arose because of the appearance of the right eye. When the parents were questioned, it was learned that the baby had been born fourteen weeks prematurely and weighed only 1,200 Gm. (2½ pounds). Five months after the first examination little change had been noted in either eye.

CASE 7.—S. N., a girl born at least twenty-six days prematurely and weighing 3,421 Gm. (4½ pounds) at birth, at the age of 4 weeks showed definite strabismus of the left eye. The parents were advised that treatment of the strabismus if it persisted had best wait until the infant was older. The mother, not being content with this advice, continued to seek treatment for the child. After a lapse of eight months it was noted that the infant did not see normally. At this time she was brought to the Massachusetts Eye and Ear Infirmary. Examination during ether anesthesia showed a relatively large, whitish mass in the fundus of each

Summary of Suggestions for Therapy

Number of Consultants	Irradiation	Diathermy	Eradication of Lens	Postponement of Operation
37 ophthalmologists	7	1	12	9
4 radiologists	3	1	0	0
4 pathologists	2	1	0	1
Total 45	12	3	12	10

eye. These masses were highly suggestive of retinoblastoma. At a clinical staff conference, opinion was divided as to the diagnosis, but as further study indicated that the left eye showed a definite increase in the size of the mass, enucleation was advised. The patient was admitted to the hospital, but bronchopneumonia developed; hence the enucleation was postponed for two months.

The pathologic specimen showed a relatively large mass of glial tissue with optic nerve fibers extending inward from the optic nerve to about 7 mm. from the back of the lens. Retina was present on each side of this mass (fig. 3). The retina in turn showed some disorganization and in places gave the impression of rosettes, a picture frequently found in sections of separated folded retina. From the apex of this mass, strands could be seen going into the vitreous in the general direction of the lens. Another such mass, of much smaller size, was seen within 3 mm. of the ora serrata on the temporal side of the globe. Here, also, strands were seen fanning out into the vitreous. In the separated retina, adherent to the glial tissue and the nerve fibers extending forward from the region of the optic nerve head, some pigment epithelium of the retina had invaded the retina proper, showing that at one time this portion of the retina was in contact with the choroid and that a mild irritation sufficient to cause invasive growth of pigment epithelium of the retina was present. Apparently tissue strong enough to exert traction on the nerve head and at another place on the retina was present, so that, with growth of the eye, the nerve fibers, retina and resulting glial tissue were pulled forward into the eye, and near the ora serrata the retina was separated.

Until case 5 was observed it was not apparent that case 7 belonged to this group. However, the fundus picture in case 5 was almost identical with the fundus picture in case 7. A review of the pathologic observations in the light of this similarity of clinical pictures led to the proper interpretation of the pathologic specimen. The pathologic observations appear to be a logical explanation of the separation of the

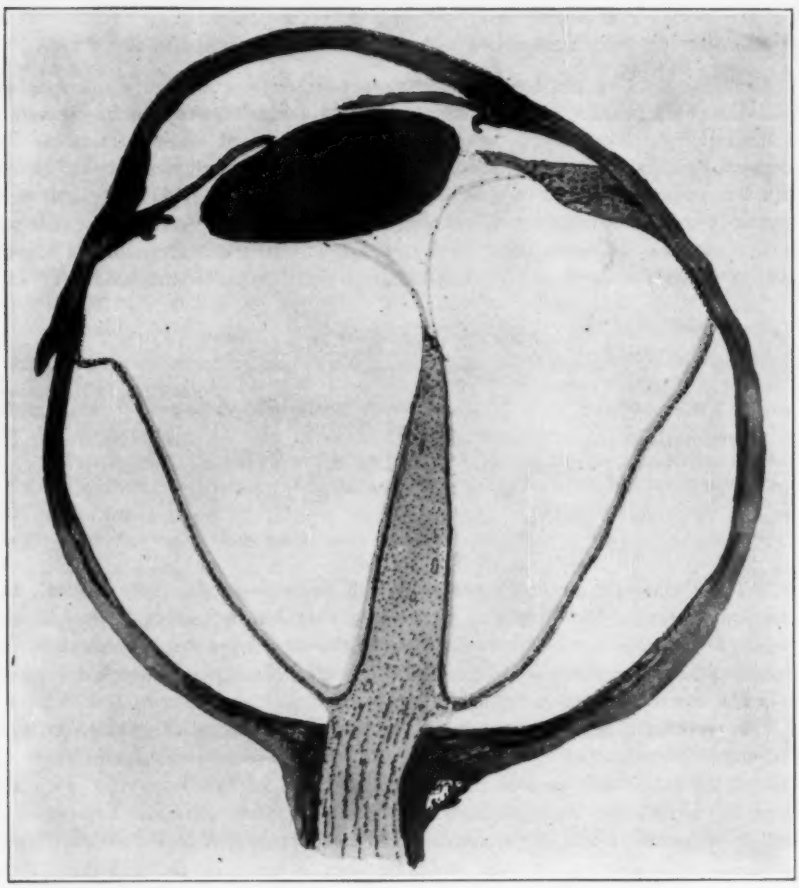

Fig. 3 (case 7).—There is no retrolental growth, but strands from back of the lens to the nerve head and to the ora serrata have pulled the optic nerve into the eye and caused retinal folds.

retina noted in certain patients and perhaps of the peculiar "chorioretinitis" in case 6. Also, there is some similarity between the processes which have produced this condition and those in the case reported by Howard.[1e] This picture can indeed account for the appearance of the retina in case 5, as well as the separation of the retina in the left eye

in case 4. This observation is in line with the findings of Dr. Charles Perera,[9] who has been impressed by the congenital separation of the retina in his group of infants with an ocular anomaly related to extreme premature birth.

COMMENT

A study of pathologic specimens available from patients with sporadic unilateral fibroplasia provides many important points if one can accept the pathologic pictures as identical with that of bilateral retrolental fibroplasia. A most interesting example is the specimen from the patient reported on by Howard [1c] in 1917 (specimen 1). A brief review of Howard's case follows:

> The somewhat microphthalmic left eye of a 5 week old full term infant was removed because of the clinical diagnosis of "glioma retinae." The anterior chamber was only 0.75 mm. deep. A posterior synechia was present, but there was no evidence of inflammation. An entropion uveae was present, in addition to an incomplete but conspicuous pupillary membrane made up of tissue identical with the iris stroma. The meshwork of the iris angle was still fetal in character. The lens lay considerably farther forward and was almost completely surrounded by persistent tunica vasculosa lentis, since a few tiny vessels were seen in the pupillary space and in the pupillary membrane, as well as in the retrolental tissue. The retina was well developed except for the fovea. The hyaloid artery was persistent. Strands resembling or identical with zonular fibers were attached to the iris and the anterior part of the retina as well as to the ciliary body. Growth of the eye and traction on the iris had distorted the iris epithelium, producing ciliary-like processes on the back of the iris. Similarly, the fibers attached to the retina had caused proliferation of glia and finger-like projections inward from the retinal surface.[10] Cortical cataractous changes were noted, as well as a continuation of low cuboid cells over the posterior surface of the lens (fig. 4).

Such retinal processes may be the reason why in case 3 the lens was pulled backward when application of diathermy to the hyaloid artery was attempted, and they may also explain why with further growth of the eye, as in case 4, a separation of the retina is produced. It is evident that the vitreous in the fetus is a fibrillar structure, as seen under the microscope, which normally becomes fiber free as it increases in bulk with growth of the eye. It should be noted that the retrolental fibroplastic membrane in Howard's case was composed of mesenchyma differentiating into fibrous tissue in which collagenous fibers had been laid down.

In another specimen (specimen 2), the retrolental fibroplasia is much less well differentiated. This eye was removed from an infant 9 days of age because of a clinical diagnosis of retinoblastoma. There is embryonic connective tissue in which collagenous fibers are less evident

9. Personal communication to the author.
10. Howard, [1c] p. 254, figure 7.

than in Howard's case. Relatively recent small hemorrhages and blood pigment from old hemorrhages are present, scattered irregularly through the newly formed tissue. However, the relatively small amount and the

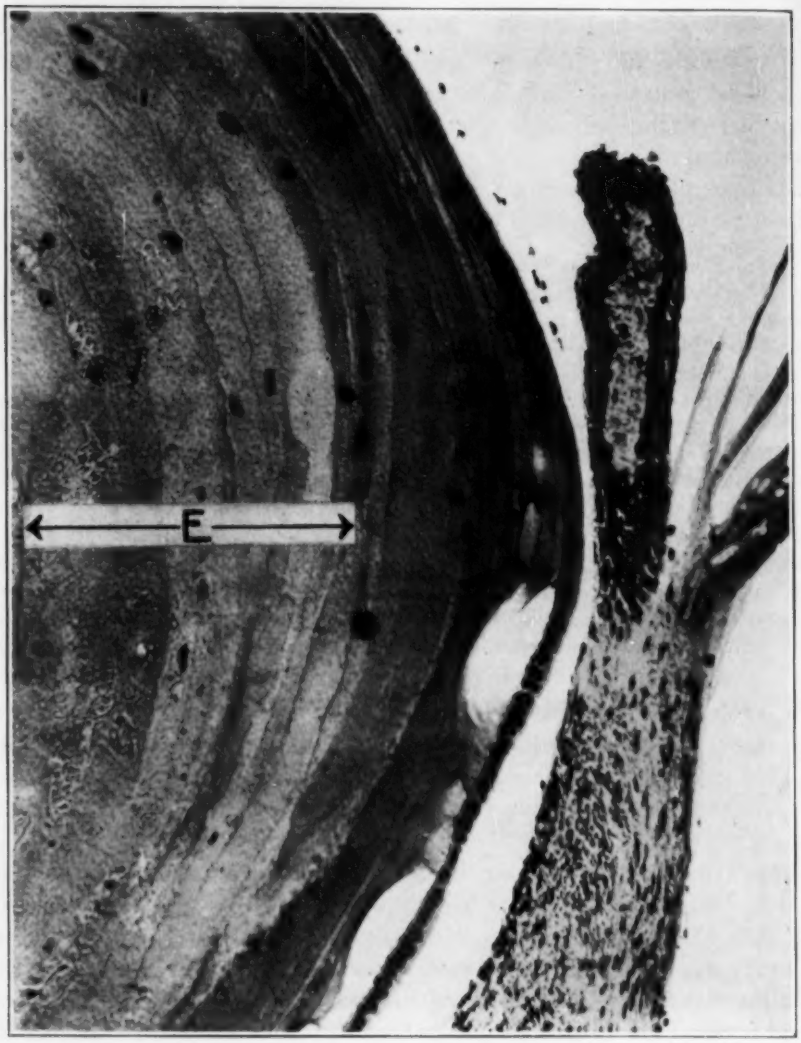

Fig. 4 (specimen 1, described by Howard [1c]).—Distortion of the ciliary processes from adherence and growth of the embryonic connective tissue. Anterior capsular epithelium extends around the equator onto the posterior surface of the lens. *E* indicates the equator.

lack of diffuse distribution suggest that hemorrhage was a result instead of a cause of the overgrowth. Again, anterior caspular epithelium is to be seen over the posterior surface of the lens. This eye has a shallow

anterior chamber also, and in it too the retrolental membrane is firmly adherent to ciliary processes, with consequent stretching and distortion of the processes (fig. 5). In fact, the dentate processes observed in the clinical cases reported doubtless represented attachment to the ciliary procesess and open spaces between these attachments. The thickness of this mass is impressive and discouraging to one desirous of removing the tissue surgically, because of the possibility of producing disastrous hemorrhages and evulsion of the ciliary processes, if not separation of

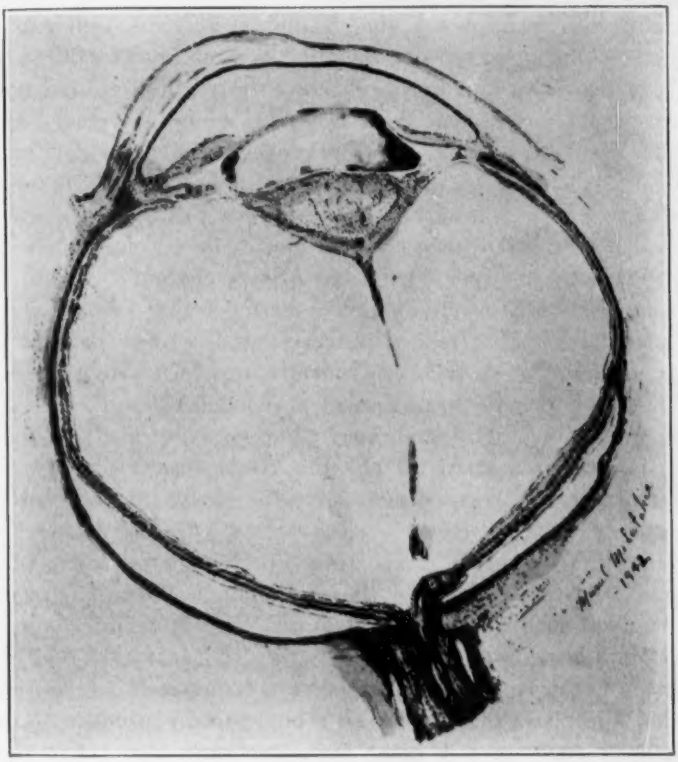

Fig. 5 (specimen 2).—Composite drawing from sections of the eye, showing a large mass of embryonic connective tissue, distortion of the ciliary processes, the retina far forward on the ciliary body and a persistent hyaloid artery.

the retina as well, since the retina is so far forward on the ciliary body at this stage of development. Also, one wonders what effect such distortion of ciliary procesess might have on the aqueous-producing capacity. A few lymphocytes and plasma cells are to be seen in the fibroplastic tissue.

In a third specimen it is evident that the retrolental fibroplasia was instrumental in rupturing the lens capsule, and the lens material has

been largely absorbed. Collins [1b] reached the erroneous conclusion that the lesion was primarily a lack of lens capsule posteriorly and the fibroplasia a reparative process. Lymphocytes are evident in this moderately well differentiated membrane also. An old, moderately small hemorrhage is present in one part of the membrane.

In a fourth pathologic specimen the picture is that of inflammation in the retrolental membrane sufficient to produce the picture of endophthalmitis. Here the lens has been largely absorbed after rupture of the capsule, as in the third specimen.

A fifth specimen shows the result of surgical removal of the membrane. One observes not only the typical fibroblastic membrane but ciliary processes and parts of retina. The child from whom this specimen was removed had what appeared to be a typical congenital cataract. The first needling was uneventful. Only during the second needling did the surgeon encounter a membrane too tough to be cut even with two discission knives. The surgeon then opened the eye and performed a so-called cataract extraction. The specimen consisted of typical retrolental embryonic connective tissue containing recent hemorrhages and small tags of ciliary processes and retina (fig. 6). In spite of the removal of some ciliary processes and retina, the eye, though blind, of course, had a relatively normal appearance two years later. Should one not then be suspicious of all congenital cataracts which on needling present a tough membrane? Cannot a fibroplastic membrane, in turn, be an explanation of why the visual results of extraction of congenital cataracts are so discouraging, as shown in statistics on the blind? [11]

From the Army Medical Museum other specimens were obtained, which ran true to the form of those already described. However, it should be mentioned that one, accession 55795, was from a patient with bilateral fibroplasia.

Perhaps I may be permitted to mention some other cases of bilateral retrolental fibroplasia that have been brought to my attention. Chandler and Verhoeff each have 1 case. Dr. Benjamin Sachs has seen the condition in an infant born at full term. The director of the Perkins Institute knows of an infant born prematurely with this condition. Dr. E. V. L. Brown wrote of another case, that of the daughter of a physician who served his residency in Chicago but has since moved to Boston. This child, born prematurely, had pathologic changes in each eye suggestive of retrolental fibroplasia in which inflammation had occurred, but the possibility of Toxoplasma as an etiologic factor has

11. Cowan, A., and English, B. C.: Causes of Blindness in Pennsylvania: Analysis of Blindness in over Thirty Thousand Eyes, Arch. Ophth. **26**:797 (Nov.) 1941.

not been ruled out conclusively. Dr. Herman Goldberg, of Baltimore, wrote of 6 cases, and the 3 cases of Dr. Charles Perera, of New York, have already been mentioned.

To learn what would be the best line of treatment, an extensive investigation is being carried out.[12] Communication with several ophthalmologic centers brought many and varied opinions, summarized in the accompanying table. These were most interesting, and the suggestions were extremely helpful. Chief among them were suggestions as to irradiation, with either roentgen rays or radium, in doses ranging

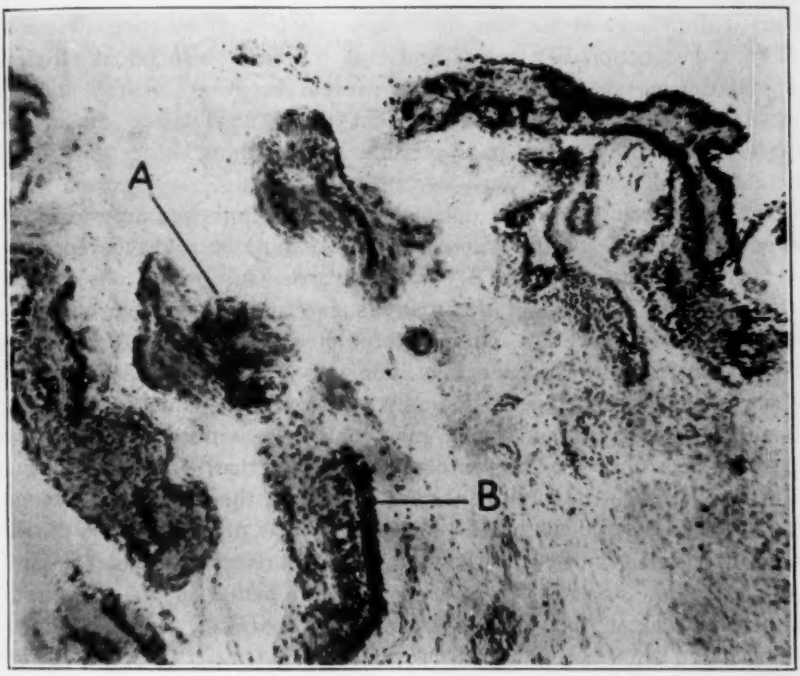

Fig. 6 (specimen 5).—Specimen removed at "cataract" extraction, consisting of embryonic connective tissue containing recent hemorrhages and small tags of ciliary processes (*A*) and retina (*B*).

from a mild erythema dose to amounts productive of vascular closure. The frequency of these suggestions gave considerable weight to the decision to use roentgen rays in case 2. Although the results were unsatisfactory, in all fairness to this type of treatment it must be remembered that both the treated and the untreated eye became worse and that glaucoma developed in each eye. Therefore, I do not feel that roentgen treatment can be condemned.

12. Terry.[3] This will also be discussed further in a later paper.

Suggestions as to surgical intervention were interesting. Certainly removal of the membrane bodily is not to be considered, but the opening of a "trap door" in the membrane, as first described by Thompson,[13] is perhaps the most logical direct attack. He reported successful operations in such cases based on cutting a trap door in the center of the membrane after the lens was removed and pushing the door flap back into the vitreous. The possibility of sealing the blood vessel behind the membrane by means of diathermy was suggested by Dr. W. P. Beetham,[9] of Boston. The attempt in case 3, in which the eye perhaps was already hopelessly blind, is not a fair test of this operation. However, it did demonstrate that diathermy can be applied to the vitreous without destruction of the eye and that a tissue of sufficient strength to pull the lens backward bodily is present between the lens and the nerve head. It indicated further that the opaque tissue must have appreciable depth and must be considered something more than just a membrane.

The suggestion to await delayed involution indicates the most conservative and perhaps the wisest course. It must be remembered, however, that 1 infant (patient 2) became worse while under observation.

A detailed analysis of the many suggestions submitted would be interesting but too long. Dunnington[9] observed 2 cases of unilateral fibroplasia, in 1 of which an operation was performed and in both of which glaucoma developed. Dunphy[9] observed a spontaneous hemorrhage in a case of unilateral involvement. Sanford Gifford[9] has operated in a few cases, never obtaining better than 8/200 vision, and in a case in which the pupil could not be dilated, the simplest iridectomy was followed by phthisis bulbi. Kronfeld[9] knew of 2 unpublished cases in which vision of not better than counting of fingers at 1 foot (30 cm.) was obtained. Evans[9] cautioned against hemorrhage. Samuels[9] cautioned against the danger of retinal separation as a result of operation in such cases. Gradle[9] said that he prefers not to operate before the age of 7, not fearing the possible lack of vision when operation is postponed. One native New Englander[9] wrote, "We can give you only our sympathy."

SUMMARY

1. The syndrome presented is composed of widespread changes consisting in primary and secondary manifestations related to: (*a*) persistence of the hyaloid artery and tunica vasculosa lentis, (*b*) growth of embryonic connective tissue behind the lens and (*c*) persistence of fetal fibrillar vitreous.

2. This syndrome is observed rarely in full term infants, in whom it is usually noted soon after birth and is almost invariably unilateral.

13. Thompson, G. W., cited by Collins.[1b]

3. It is observed more frequently in infants born extremely prematurely. It is usually noted four to six months after birth and is almost invariably bilateral.

4. When the condition is first seen, the diagnosis is not always obvious. It must be differentiated from retinoblastoma as well as from congenital cataract.

5. Glaucoma is an important complication.

6. Treatment has involved (*a*) temporization, (*b*) irradiation and (*c*) closure of the hyaloid artery by diathermy.

7. Surgical treatment by complete removal of the membrane seems unwise, since pathologic specimens show that ciliary processes and retina are adherent to the fibroplastic membrane.

8. A surgical approach by cutting a hole in the membrane has been reported.

9. Intraocular hemorrhage and inflammation were found in the embryonic connective tissue in some of the pathologic specimens obtained from patients with unilateral involvement.

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FIBROBLASTIC OVERGROWTH OF PERSISTENT TUNICA VASCULOSA LENTIS IN PREMATURE INFANTS

IV. ETIOLOGIC FACTORS

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A new syndrome of ocular maldevelopments in infants born prematurely has been reported previously.[1] No conclusive statement can be made at this time as to the exact cause or causes of this entity. However, a discussion of the various etiologic factors, stressing the theory that now appears most logical, is of value in bringing the problem to the attention of many observers. By this means the solution may be arrived at more quickly, with regard not only to the most satisfactory preventive measures but to the best treatment, perhaps soon enough to be of practical value for infants now under observation.

This syndrome, consisting primarily in bilateral fibroplasia, is based on: (1) persistence of some part of the tunica vasculosa lentis system, (2) growth of embryonic connective tissue behind the crystalline lens and/or (3) persistence of the fibrillar structure of the vitreous humor. It has been pointed out [1c] that the condition is more than a persistence of the tunica vasculosa lentis, which consists only in the arborization of small branches and does not carry with it any connective tissue. Furthermore, the vitreous is fibrillar only while blood vessels are present.[1c]

The predisposing cause of bilateral development of the condition appears to be premature birth at a stage early enough for the hyaloid artery, with its tunica vasculosa lentis and pupillary membrane, to be patent. The degree of prematurity appears to influence the severity and the distribution of the various maldevelopments, the retinal folds with tractional "pseudopapilledema" being most pronounced in the infant born least prematurely and the fibroplasia in the infant born most prematurely.

In full term infants the condition is usually unilateral and is present at birth. The appearance of the eye is definitely abnormal, conspicuous enough to be observed by the parents. The unilateral condition, then, must develop in intrauterine life before the hyaloid arterial system

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Read before the Section on Ophthalmology at the Ninety-Third Annual Session of the American Medical Association, Atlantic City, N. J., June 11, 1942.

1. Terry, T. L.: (*a*) Am. J. Ophth. **25**:203, 1942; (*b*) Tr. Am. Ophth. Soc., to be published; (*c*) Am. J. Ophth., to be published.

disappears.[1c] In all the cases in my series of bilateral fibroplasia in infants born prematurely, the abnormality of the eyes was not observed until the infant was from 4 to 6 months of age. The condition in the prematurely born infant, then, must develop largely, if not entirely, after birth.

The exciting cause may be the same, acting before birth in the full term infant and after birth in the premature infant. It must be borne in mind that this exciting factor may be present for only a few minutes or for a few hours, but, the process of fibroplasia having started, it may act as a vicious cycle, resulting in a severe aberration of development.

Heredity does not appear to be concerned. The disease may involve only one of twins, and there has been no history of abnormal vision of a hereditary nature in any of the families in which it has been observed.

Prenatal factors of etiologic importance in the premature infants were not obvious from the mothers' histories, although detailed records were available in only 2 instances, since in the remaining cases the mothers had no recorded antepartum care. The cause of prematurity was not invariably evident. In 1 case the mother was under treatment for bacilluria, and in another case the mother had had throughout pregnancy periodic uterine bleeding of a type she thought did not differ from her usual menstruation. It is possible that the cause of the prematurity may have been the exciting factor. However, since the condition was not evident until four to six months after birth in the premature infants and was evident at birth in the full term infants, a factor causing premature birth would not explain the occurrences in all instances. In some cases the cause of the prematurity was related to multiple pregnancy. Hess [2] stated the belief that multiple pregnancy is the most common cause of premature labor. The incidence of twins in the present series of premature infants (3 among 7 infants) is much higher than the usual average (about 16 per hundred premature births [2]). Twinning tends to cause a lowering of the vitality, and this may have some significance in stimulating any other deleterious factor. Search for use of the more recent drugs, such as the sulfonamide compounds or perhaps soluble pentobarbital, showed no evidence that a drug had been used uniformly. In 1 instance sulfanilamide and later sulfadiazine (2-[paraaminobenzenesulfonamido]-pyrimidine) were administered to the mother after parturition, and the infant (patient 1), being given breast milk, could possibly have been affected by these drugs.[3] New

2. Hess, J. H.; Mohr, G. J., and Bartelme, P. F.: The Physical and Mental Growth of Prematurely Born Children, Chicago, University of Chicago Press, 1934.

3. Hac, L. R.; Adair, F. L., and Hesseltine, H. C.: Am. J. Obst. & Gynec. **38**:57, 1939.

drugs are stressed, because if they were of etiologic importance, then the explanation would be apparent as to why this disease was not recognized earlier. From a review of the prenatal histories,[1b] no common prenatal factor could be established.

The processes of birth itself in the premature must be considered. Certainly trauma could be of importance, or partial asphyxia resulting in hemorrhages. Although the infants were all extremely small and not subjected to the trauma at birth of a full term infant, still small amounts of trauma are productive of hemorrhages in these more immature infants.[3] However, in case 1 at least, if a bilateral retrolental hemorrhage had occurred it would have been observed, as no fundus reflex would have been seen.[1b] Perhaps it is possible for partial asphyxia or trauma at birth to cause retrolental hemorrhages when the hyaloid artery and tunica vasculosa lentis are still present. According to Ross and Mallory,[4] newborn infants showing asphyxia suffer more frequently from spontaneous hemorrhage than normal infants. In the eyes of fetuses, small hemorrhages in the tunica vasculosa lentis are not uncommon; in fact, hemorrhages were found in 5 human fetal eyes out of the 50 studied by serial section. In only 2 instances were the hemorrhages bilateral. Of course it must be remembered that death was probably from asphyxiation. Hemorrhages were found more frequently in the eyes of pig fetuses than in those of human fetuses, and the pig fetuses had invariably died of asphyxiation. Although the pigs were not subjected to the trauma of birth, in approximately one half of the fetal pig eyes examined, hemorrhages were present. The hemorrhages in the human fetal eyes were never bilaterally symmetric and were never large (fig. 1). They were found as often deep in the vitreous or near the optic nerve as immediately behind the lens, where they undoubtedly would be to produce the typical lesions. It is possible that certain physical or physiologic factors may be present in the hyaloid system which would produce bilateral retrolental hemorrhages. These might be caused by asphyxia or by trauma of a degree sufficient to produce hemorrhage only in vascular structures that are in the process of regression and in which the vessel walls are weakened.

Vitamin K deficiency as an essential factor was suggested.[5] A deficiency of this vitamin could produce intraocular hemorrhages, which in turn, through organization, would give rise to the lesion. It had been suggested previously[6] that bilateral retrolental hemorrhages as part of asphyxia or trauma at birth could be of etiologic importance. Certainly in the pathologic specimens[1b] variable amounts of blood pig-

4. Ross, S. G., and Mallory, H. T.: Canad. M. A. J. **45**:417, 1941.

5. Goldberg, H.: Personal communication to the author. Goldberg has observed 5 infants with fibroplasia, concerning whom he wrote after seeing my preliminary report of the condition.[1a]

6. Clifford, S.: Personal communication to the author.

ment and hemorrhage were present. However, contrasting of the pathologic picture of fibroplasia with that of true cyclitic membrane formation in the adult eye following inflammation or hemorrhage shows certain differences. The tissue of retrolental fibroplasia is embryonic connective tissue, while the cyclitic membrane is made up of true scar tissue. In distribution, the embryonic connective tissue follows uniformly the curve of the lens, reaching almost invariably to the equator of the lens, to which region the attached ciliary processes are pulled in a typical deformity. The cyclitic membrane is limited to the posterior

Fig. 1.—Section of eye from a 93 mm. human fetus. A hemorrhage is seen near the equator of the lens (see arrow). This is the largest hemorrhage found in any of the human fetuses. Because of its small size, it would not be prone to call forth as massive an organization as would be seen in even the less serious forms of fibroplasia.

surface of the lens. It does not reach the equatorial region unless it has a continuation past the equator to surround the anterior surface of the lens as well. Separation of the retina, common in both conditions, occurs in fibroplasia through traction of persistent strands of fibrillar vitreous, which adhere firmly to the retina, thus producing rounded (case 4), conical (case 7) or foldlike (case 5) separations, which may result finally in complete retinal separation of a somewhat irregular umbrella shape. In cyclitic membrane formation the retinal separation

begins through traction of contracting connective tissue attached at or behind the ora serrata, giving rise to a peripheral separation of the retina first. Moreover, though the cyclitic membrane may be vascularized, the channels are obliterated as the scar tissue contracts, whereas remains of the hyaloid artery and posterior portion of the tunica vasculosa lentis are uniformly present in the specimens available.

Against the theory of hemorrhage with vitamin K deficiency as the essential cause, it must be mentioned that in case 1 a normal fundus reflex was observed in each eye, even at the age of 76 days, although no vitamin K was administered. Any possible hemorrhage present in the vitreous, therefore, would have been small and peripherally placed. However, in case 5 vitamin K was administered and yet the amount of retrolental fibroplasia was less than in any other case in the series. In this case intracranial hemorrhages were diagnosed shortly after birth.[1b] This diagnosis was confirmed by the presence of xanthochromic color in the spinal fluid. Also, the twin of the patient died shortly after birth, and intracranial hemorrhages were confirmed by a postmortem examination. Several other infants in the series had received vitamin K therapy. In case 2 the retrolental fibroplasia was pronounced in spite of administration of vitamin K for three days after birth.

Factors occurring after birth which might be of importance are certainly more numerous and perhaps more logical as etiologic factors. An attempt has been made to evaluate some of the physiologic changes incident to the adaptation to extrauterine life, especially in relation to prematurity.

Self regulation of bodily temperature, with related changes in bodily metabolism, is certainly one important consideration. At birth the premature infant is incompletely homothermic. All higher Mammalia which are homothermic appear to go through stages of poikilothermism in their early development.[7] Premature infants must be maintained in surroundings carefully regulated as to temperature and humidity,[8] and since, unlike the opossum pouch young,[9] they are only incompletely poikilothermic, attempts to maintain a bodily temperature normal for adults tend to result in hyperpyrexia. This change in temperature[10]

7. Needham, J.: Chemical Embryology, London, Cambridge University Press, 1931, vol. 3.

8. Blackfan, K. D., and Yaglou, C. P.: Premature Infant, Am. J. Dis. Child. **46**:1175 (Nov., pt. 2) 1933.

9. McCrady, E.: Embryology of the Opossum, Philadelphia, Wistar Institute of Anatomy and Biology, 1938.

10. To evaluate some of the factors which might be involved, experiments are being carried out with (1) variations in temperature, (2) variations in light, (3) vitamin deficiency, (4) decrease in the oxygen-carrying powers of the blood

is also a factor that cannot be disregarded. A few degrees of difference in bodily temperature might influence the continued differentiation and development of the prematurely born infant and in theory, at least, could affect the development and regression of the tunica vasculosa lentis.

Premature exposure to light has impressed many of the physicians with whom this problem has been discussed. Held [11] pointed out that exposure to light is a stimulus to completion of myelination of the optic nerve. Salzmann [12] observed that myelination of the optic nerve is proportional to the period of postnatal life in the premature as well as in the full term infant, so that premature exposure to light, even through the thin eyelids, does influence ocular development. In fact, experiments not yet complete [10] in which excessive exposure to light was given were followed by variations in the time of regression of the hyaloid arterial system.

Premature loss of certain materials supplied through the placenta from the mother before the infant is able to fill its own needs can well be of great etiologic importance. For instance, adult ovarian hormones may be necessary for normal regression of the hyaloid artery and tunica vasculosa lentis. Even if the infant is a female, her own immature ovaries would not be providing the same hormonal influence as the ovaries of the pregnant mother. It appears that the fetus is self sufficient in regard to insulin and pituitary secretion, that thyroxin is not abundant and that epinephrine is not elaborated until birth.[7] All hormones should be considered further. The infant born prematurely may be unable to digest and absorb foodstuffs comparable to the nourishment supplied through the placenta. Although insufficient digestion may cause the retrolental fibroplasia affecting the infants most deficient in this respect, in the one set of surviving twins (case 2) [1b] the better developed and more vigorous of the two rather than the weaker had the

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by exposure to carbon monoxide and by feeding of sulfanilamide, (5) intraocular injection of blood, (6) graded constriction of the neck and (7) injection of pressor and depressor substances to vary the blood pressure. As a therapeutic measure of possible value, the sulfuric acid ester of hyaluronic acid was injected into eyes of opossum pouch young in which the hyaloid arterial system was still present, to determine whether this would stimulate a precocious closure of the arterial system. This ester was supplied by Dr. Karl Meyer, of the Eye Institute, New York. Animals were chosen for the experiments whose young had a patent hyaloid arterial system at birth. The opossum has been used in many experiments, because, since it is a marsupial, the young are born in a very immature stage. Pregnant and newborn rats, cats and pigs have also been used. To date none of the experiments has gone far enough to enable me to report scientifically significant results. However, several trends of interest, one of possible therapeutic value, have been noted.

11. Held, R.: Arch. f. Anat. u. Entwcklungsgesch., 1896, p. 222.

12. Salzmann, M.: Anatomy and Development of the Human Eyeball, translated by E. V. L. Brown, Chicago, University of Chicago Press, 1912, p. 208.

fibroplasia. In regard to insufficient digestion and assimilation of foodstuffs, all vitamins would be a necessary consideration. Special mention of vitamin K (previously discussed) and riboflavin should be made. A deficiency of the latter [13] appears to stimulate abnormal growth of the blood vessels.[14]

Other rather dramatic changes incident to birth are related to the blood. The characteristic blood group does not show itself until after birth. It is possible that removal of the fetus from the direct effect of the mother's blood allows the infant's blood to take on its own hereditary characteristics at an earlier stage. Although this factor might be of importance in the causation of retrolental fibroplasia, its effect is not easily evident. In infants born either at full term or prematurely, the number of red blood cells and the percentage of hemoglobin show high values, which are gradually lost as more efficient aeration through the lungs and improved circulatory efficiency make it unnecessary for the organism to have so many red blood cells. In the premature infant the value for whole blood iron and that for hemoglobin decrease after birth, to reach their lowest levels after eight to twelve weeks. Evaluation of the extent of the anemia in an infant in whom fibroplasia later developed was possible only in case 1, in which the hemoglobin increased before the erythrocytes reached their lowest value. Erythroblastosis and its apparent relation to differences in the RH factor must be evaluated. Data are being collected on this series [1b] which to date have revealed 2 cases in which the mother showed a negative RH factor while the child showed a positive one.[14a]

Precocious increase in blood pressure [10] in the fetus in utero or in the infant born prematurely as an etiologic factor is indeed worthy of close consideration. After birth the systolic pressure gradually rises for the first ten days,[15] even in the premature infant, from such factors as crying,[2] feeding [2] and increased bodily metabolism. An abnormal increase in blood pressure has been found after dehydration and administration of drugs.[15] A sufficient increase in blood pressure while the hyaloid system is still functioning would delay involution, if not cause an overgrowth, of this vascular system. As fibroplasia develops in only a small percentage of prematurely born infants, only those who have the highest blood pressure would acquire the disease, its relative infrequency thus being explained. Variations in the systolic blood

13. In an article published after this paper was read, R. M. Calder stated that ariboflavinosis is a cause of increased blood pressure in rats (J. Exper. Med. **76**:1, 1942).

14. Bessey, O., and Wolbach, B.: J. Exper. Med. **69**:1, 1939.

14a. From the Blood Grouping Laboratory of the Children's Hospital.

15. Woodbury, R. A.; Robinson, M., and Hamilton, W. F.: Am. J. Physiol. **122**:472, 1938.

pressure of premature infants do exist, as shown in reports on specific patients by Hess.[2] In girl G of his series the systolic pressure rose from 47 to 57 mm. in twenty days, whereas in baby B it rose from 28 to 65 mm. in the same period.[16] The stage of prematurity [15] and the increase in weight [2] appear to have a correlation with the blood pressure.

Patent ductus arteriosus and foramen ovale can be factors in altering the blood pressure. In case 3 there were indications of a congenital cardiac defect consisting in a ventricular septal opening. It is to be presumed that the ductus arteriosus in all infants is open for a variable period,[17] and it may remain open in infants born prematurely longer than in infants born at full term. There is a reversal of the circulation through the ductus when it remains open, from the aorta to the pulmonary artery, so that a considerable portion of the blood from the left ventricle is short-circuited by way of the ductus arteriosus through the lungs and back to the left atrium. This leads to considerable overwork of the left side of the heart and an alteration in the quantity of blood to various parts of the body, as illustrated by a higher systolic pressure in the arm than in the leg.[18] It has been postulated [19] that in the event there is less flow of blood through the splanchnic region there may be more flow through the head.

An abnormal increase in fetal blood pressure in utero must occur at times. It could result from passive congestion in the head through sublethal constriction on the neck [10] caused by a loop of the umbilical cord. If applied asymmetrically it could produce somewhat unilateral passive congestion, thus explaining the more frequent origin of unilateral fibroplasia in the full term infant.

The existence of increased blood pressure would not prove conclusively that arterial hypertrophy would be produced in the prematurely born infant. In fact, in young adults in whom coarctation of the aorta had been present for some time and in whom the systolic pressure averaged 70 mm. higher in the arm than in the leg, no arterial or arteriolar hyperplasia or sclerosis could be detected by biopsy of skin and voluntary muscle.[20] However, it has been observed that the walls of blood vessels do hypertrophy and atrophy in response to considerable changes in blood pressure in other conditions. This fact is graphically

16. Hess,[2] figures 66 and 67, p. 284.

17. Patten, B. M.: Anat. Rec. **35**:129, 1931. Christie, A.: Normal Closing Time of Foramen Ovale and Ductus Arteriosus, Am. J. Dis. Child. **40**:323 (Aug.) 1930.

18. Eppinger, E. C.; Burwell, C. S., and Gross, R. E.: J. Clin. Investigation **20**:127, 1941.

19. Wislocki, G. B.: Personal communication to the author.

20. Graybiel, A.; Allen, A. W., and White, P. D.: J. Clin. Investigation **14**:52, 1935.

illustrated by the hypertrophy of the veins in the immediate vicinity of abnormal arteriovenous communications in response to the greater blood pressure to which they are subjected and likewise by the atrophy of

Fig. 2.—Cross section (15 microns) of hyaloid artery from a 9 day old infant with unilateral fibroplasia. The wall of the vessel is severely hypertrophied.

the arteries in the same region when the blood pressure is considerably reduced by the existence of the so-called aneurysm.[21]

21. Reid, M. R.: Abnormal Arteriovenous Communications, Arch. Surg. **11**:25 (July) 1925.

A study of the walls of the vessels in specimens of unilateral fibroplasia showed definite hypertrophy and even sclerosis (figs. 2 and 3). These conditions were perhaps first noted by Haden.[22] When he saw

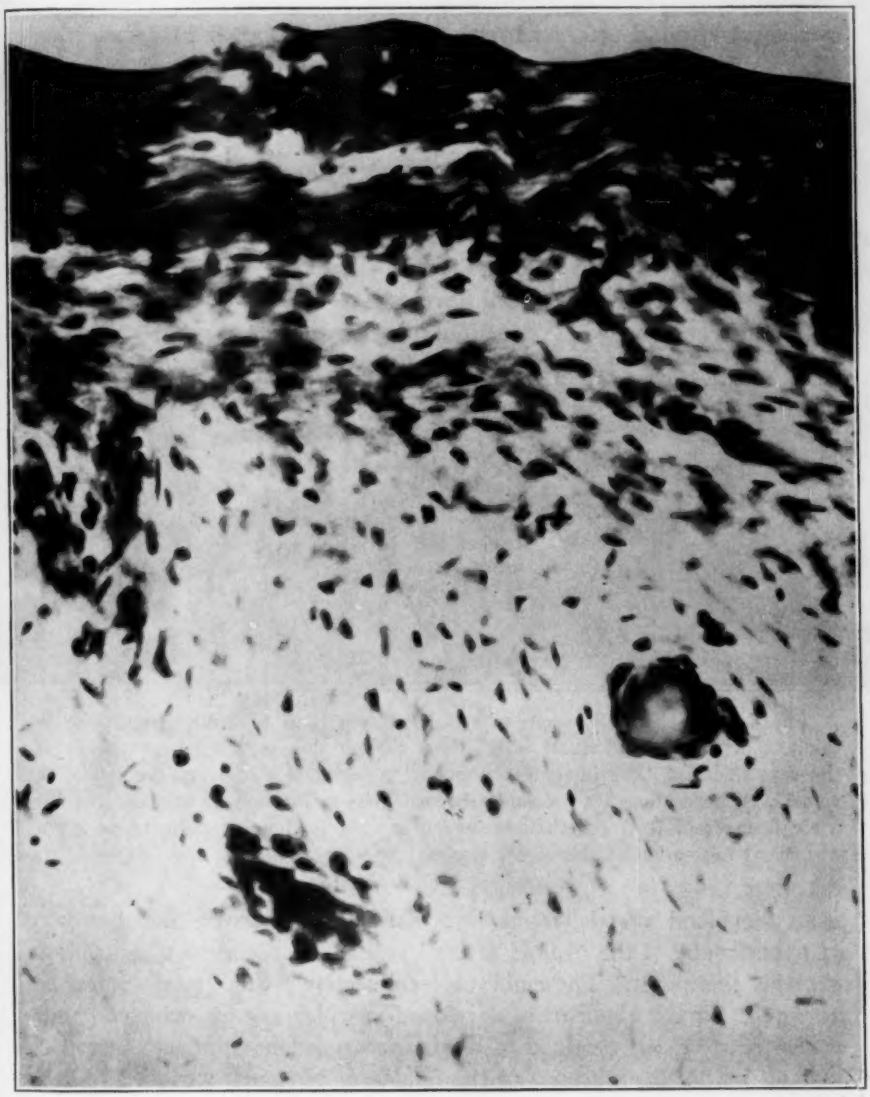

Fig. 3.—Smaller branches in the retrolental fibroplasia, also showing hypertrophy, of the infant represented in figure 2.

the most dramatic of the specimens he was impressed that the vessels in the retrolental mass did not appear to be capillaries. On this fact

22. Haden, H. C.: Personal communication to the author.

he based the opinion that these vessels could not be those of the tunica vasculosa lentis, which is normally composed of capillaries. The difference between the vessels in fibroplasia and in the normal fetus eye as studied in sections is pronounced. In fibroplasia the walls of the persistent hyaloid artery and its branches are from 3 to 5 cells thick (fig. 4). A precocious increase in blood pressure in the hyaloid system occurring at the proper time could result in this hypertrophy and even in relative sclerosis.

Just how a retrolental growth of embryonic connective tissue would arise because of an increase in blood pressure and in blood flow was not visualized early in the study. An increased blood supply ordinarily prevents fibrosis, if one is to judge from the observation that the richer pattern of blood flow may itself have considerable to do with the differentiation of mesenchymal tissue into muscle, whereas at greater distances

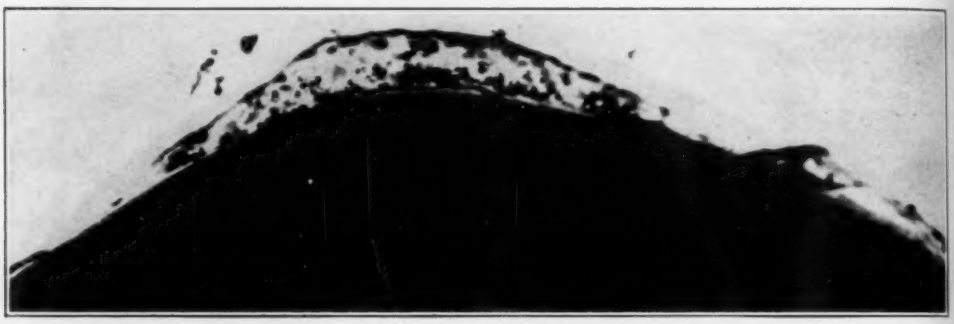

Fig. 4.—Vessel near the lens in a 220 mm. pig fetus (100 microns). Note the thinness of the normal vessel wall. Even though this section was cut over six times as thick as those in figures 2 and 3, to facilitate model reconstruction, the vessel wall here, though not completely analogous in location, is composed of only a single layer of fetal endothelium, which in turn is showing thinning as a part of normal regression of the vessel system.

from the blood vessels, fascia is produced.[19] However, the discovery of hypertrophy of the hyaloid arterial system in specimens of fibroplasia explains this point. The embryonic connective tissue grows to furnish a support for the abnormally developed vascular system, which as thin-walled fetal vessels destined to disappear needed no support other than that of the fibrillar vitreous of the fetal eye. In turn, variations in the amount of the retrolental fibroplasia can be determined by the richness or the paucity of the vascular system when abnormally high blood pressure arises.

As this viewpoint appears the most logical explanation of all phases of the fibroplasia, it is offered here as the preferable etiologic theory.

SUMMARY

A search for the essential etiologic factor or factors causing fibroplasia both in infants born prematurely and in infants born at full term has been made with due regard to the possibility that the disease in its full development may represent the culmination of a vicious cycle initiated by an essential cause in effect for a limited and perhaps brief duration.

Prematurity, often with twinning, is an important predisposing, but not invariably an essential, factor, and the degree of prematurity appears to influence the nature of the involvement.

The factors considered are grouped as hereditary, prenatal, natal and postnatal, and variable factors of perhaps subsidiary importance are also discussed: i. e., cause of prematurity; use of new drugs; trauma or intraocular hemorrhage introducing the process; incomplete homothermism; premature exposure to light; premature loss of certain materials, such as hormones, supplied through the placenta from the mother; incomplete digestion and assimilation of foodstuffs, causing a deficiency, for example in riboflavin, and changes in the blood, such as a premature establishment of the characteristic blood group, physiologic anemia of prematurity and erythroblastosis with differences in the RH factor.

The outstanding theoretic cause is a precocious increase in blood pressure brought on before the hyaloid artery and the tunica vasculosa lentis disappear, initiated by such normal factors as adaptation to extrauterine life or such abnormal factors as patent ductus arteriosus, dehydration or use of drugs.

After the development of increased blood pressure, hypertrophy of the hyaloid arterial system takes place, causing persistence of fibrillar vitreous and growth of a support of embryonic connective tissue.

243 Charles Street.

ABSTRACT OF DISCUSSION

Dr. Parker Heath, Detroit: A point stressed in Dr. Terry's most interesting paper is prematurity. It should be clear that full term infants may be seen who show bilateral postlental membrane or mesenchymal proliferation. The single factor of prematurity is not sufficient to explain their anomaly.

If one scans the literature, one can find references as far back as 1882; for example, an article by Meyerhausen, wherein this condition in rabbits was reported. The anomaly has been reported in other animals, including tigers. So, the condition is not new in comparative ophthalmology. It is rare in practice.

One is apt to get an attitude of defeatism because of the subsequent developments. In the first place, practically all the patients show either undifferentiated retina or detachment of the retina due to the shrinkage and pulling of the prolongations through the vitreous.

Dr. Terry has enumerated many etiologic factors and obviously is unable to come to concrete conclusions.

The best suggestion he has offered, backed by objective findings, is the permanent changes in the fetal vessels, infantile sclerosis. All sufficiently premature infants show the hyaloid artery. The fact that the hyaloid artery is present at birth to such an extent is pathologic only in the full term child.

There is one factor Dr. Terry did not mention which seems to me important. One occasionally sees a patient in whom the remnants of lens have become disklike and in whom there is a thickening of the posterior capsule, or proliferation and partial absorption. One can sometimes help such patients by cutting a window through the disk with scissors, being careful to avoid any trauma by pulling. The benefits are proportional to the amount of differentiation of the retina and the possibility of detachment.

In general there is no advantage in early treatment to prevent amblyopia, because the best vision such patients get is below the level of that obtained with an amblyopic eye.

I shall illustrate on the screen what seemed to be an intermediary stage between the bilateral condition of the premature infant and that of a full term baby. In this case there was the characteristic small eye, which is an important differential sign, and a retrolental increasing grayish vascular mass on the mesial side. The other eye, incidentally, showed an anomalous arrangement of blood vessels on the nerve head. In addition there was a mass of what looked like glial tissue, the so-called primitive papillum type of tissue, on the nerve head. The baby was a full term infant. (Slides were shown.)

A clinical differential diagnosis was not so difficult if one considered the small eye, the position and character of the blood vessels, the appearance and color of the mass and the changes of altered development in the other eye.

Dr. Terry has made a good start on this problem, on which much experimental work is indicated.

It would be well for ophthalmologists to furnish him with any material they may have, so that he may have a pool of information as large as possible about this difficult subject.

Dr. Sanford Gifford, Chicago: I only wish to mention a typical case of the unilateral condition described by Dr. Terry, in which there was a large mass behind the lens, so large that it looked yellow and was considered to be a glioma. It did not permit any fundus reflex. This eye was the first one of the kind I had ever seen and was enucleated because of the possibility that the growth was a retinoblastoma.

On section it was discovered that the condition was identical with that in a case reported by Dr. Terry. I went back and looked at my notes and found that the eye was smaller than the other; that is, the cornea measured only 9 mm., as opposed to 11 mm. for the other eye.

Since then I have observed at least 4 other cases. Three of these were of the bilateral type of condition, and, so far as my notes go, the anomaly was not associated with prematurity.

The cases were referred to me for an opinion as to whether or not the growths were gliomas. In all of them the corneas were found to

measure less than normal for the age, and it seemed to me worth putting them on record, because even slight differences in size seemed to be of great diagnostic value in favor of congenital anomaly rather than glioma.

So far as I know, patients with retinoblastoma have never been noted to have any degree of microphthalmos.

I have another case that bears on the question of retinal detachment. I saw a boy with a complete, persistent hyaloid artery in one eye; vision was 22/100. A year later an almost complete retinal detachment had developed and the vision had dropped to practically nothing. I suppose these changes were due to the contraction of the bands formed on the basis of the vasa hyaloidea propria which Dr. Terry has spoken about.

Dr. Herman Goldberg, Baltimore: In addition to the observations already mentioned, I should like to call attention to the presence of keratitis and posterior synechias as a complication of this disease. The entire picture seems to become slowly, but progressively, worse.

The etiologic factor may be a lowered prothrombin level associated with a vitamin K deficiency. If a preretinal hemorrhage or bleeding from the hyaloid system did occur, the blood would gravitate into the space occupied by the primary vitreous, and the exact clinical picture Dr. Terry has described could be produced as a result of activity of retinal mesoblastic tissue.

Dr. T. L. Terry, Boston: The discussers have treated me kindly in accepting my presentation in a general way without dwelling on numerous problems in which vigorous disagreements could arise.

Dr. Heath's search of the literature with reference to the report of this lesion in rabbits and tigers is of considerable interest. It is certainly an enthusiastic scientist who may have observed the condition in living tigers.

The stressing of a disklike change of the lens by Dr. Heath is important. It has been shown in a report of these cases which I gave before the American Ophthalmological Society that a cataractous lens in 1 instance hid the retrolental fibroplasia. Only after the second discission and a pathologic study of the material removed was the true nature of the condition understood. Fibroplasia, in turn, if one may judge from a limited number of pathologic specimens, is productive of extension of the anterior capsular epithelium around the posterior surface of the lens, a condition which would prevent further growth of the lens. Thus one should expect microlentia at times.

I agree with Dr. Heath that it is certainly justifiable to remove an eye when glioma cannot be ruled out, but with the points that he and Dr. Gifford have stressed, perhaps this diagnosis should be made more accurately.

The pseudorosettes to which Dr. Heath referred can arise as an artefact through sectioning of folded separated retina perpendicularly and obliquely and need not indicate some metaplasia of the retina. Dr. Heath did not have a fair opportunity to review in exact detail my communication, because certain recent developments necessitated a last minute revision, which was not fully completed until the day before the paper was presented. He had only an original draft of the essay, and the revision

reached him so late that he had no real chance to study all of the changes leisurely and in detail.

Dr. Gifford's conviction that a small cornea is a cardinal point in a differential diagnosis is correct. The shallow anterior chamber is equally important. When the vessels do not persist in their connection with the iris, a pupillary response is present. But when those vessels do exist or adhesions result a bound-down pupil will be found.

Transillumination is of importance in the differential diagnosis. Perhaps, as Pfeiffer has pointed out, roentgenograms will show calcium in many eyes containing retinoblastoma.

I was very much impressed in examining Dr. Goldberg's patients. The opacity of the cornea is a finding new to me. The children under his care are, however, somewhat older than those I have seen. In the sections from one of the eyes which came to microscopic study, the amount of hemorrhage is extremely impressive and would lead to his viewpoint that hemorrhage related to vitamin K deficiency is of future importance etiologically. I did not find the completely typical embryonic connective tissue so characteristic of the other pathologic specimens.

RELATION OF DIET TO LENTICULAR CHANGES IN LARVAE OF AMBLYSTOMA TIGRINUM

ESTHER M. PATCH, A.M.
HADDONFIELD, N. J.

Cataracts in the tiger salamander, Amblystoma tigrinum, were first observed by me [1] in the summer of 1933 in larvae raised from Illinois eggs and used in a study of the nutritional needs of this rapidly growing larval form for the formation of bone and blood. Cortical opacities (fig. 1 *A*) with a thin subcapsular space developed in larvae fed for a month or more a semisynthetic ration containing a high level of purified casein and a smaller amount of powdered milk. The disease did not appear in animals of the same lot fed the same ration with added cystine or in those (fig. 1 *B*) fed pulverized beef muscle as a source of protein in a semisynthetic diet with different combinations of the calcifying vitamin and minerals. An early stage of the opacities was seen rarely (fig. 1 *C*) as striations from the equator to the anterior pole. The lenticular swelling was followed by shrinking until the lens was lost from view and the pupil became depressed (fig. 1 *D*). The gross changes of these cataracts resembled the progressive changes described for human cataracts of a senile nature.[2] Bilateral subluxation in one larva allowed observation of the shrinking process (fig. 1 *E* and *F*). Death of some of the larvae before identification of the cause for their feeding difficulty prevented an exact record of the percentage in which the lenticular disturbance occurred; 43 per cent was the figure listed. Although the disease was clearly nutritional, the feeding of the purified casein diet without and with cystine was repeated, while other dietary studies were being made, in 1934 with larvae raised from Wisconsin eggs of the species and in 1935 with larvae raised from Tennessee eggs. The repetition checked the original results.

When it had been shown that cataracts were produced by feeding the diet of purified casein with powdered milk to Amblystoma tigrinum of different strains, the subject of cataract was considered closed and attention was centered on other problems of salamander nutrition. It was soon found, however, that new diets being used were producing

1. Patch, E. M.: Cataract as a Result of Dietary Deficiency in Larval Amblystoma Tigrinum, Science **79**:57-58, 1934.

2. May, C. H.: Manual of the Diseases of the Eye for Students and General Practitioners, revised with the assistance of C. A. Perera, ed. 17, Baltimore, William Wood & Company, 1941.

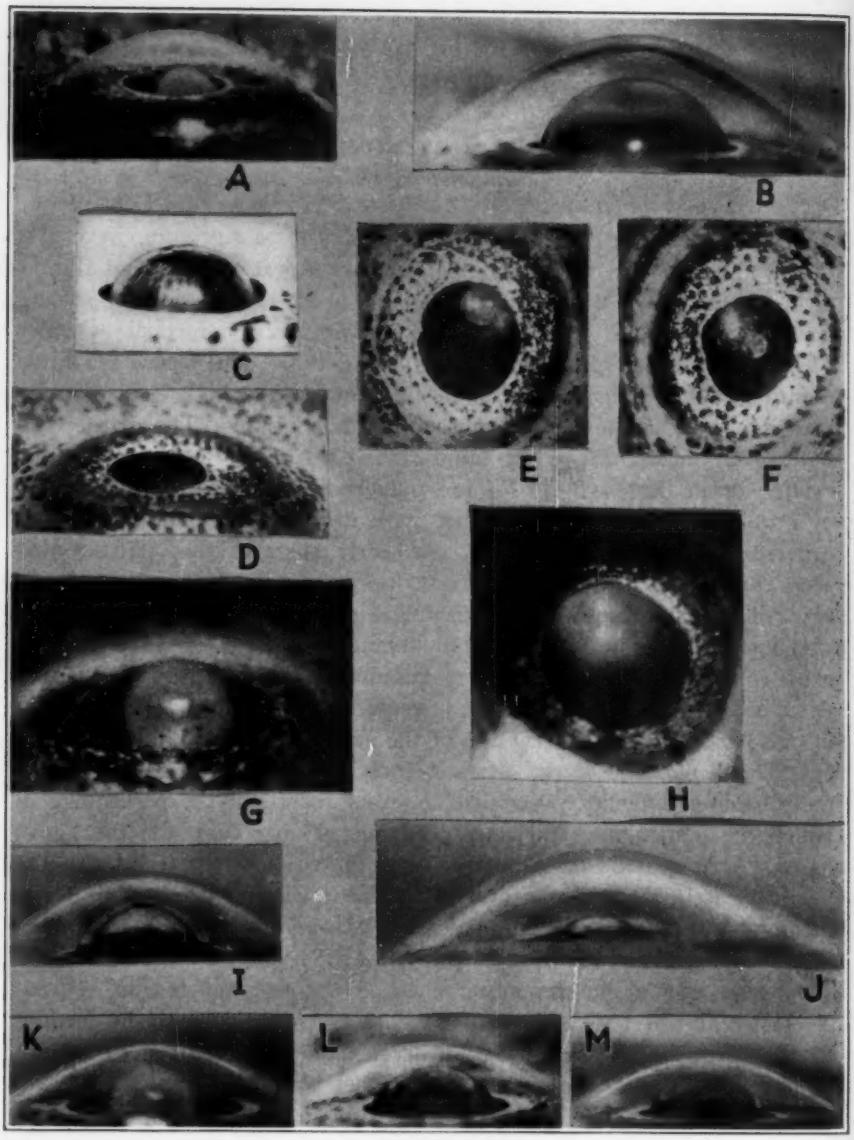

Figure 1

(See legend on opposite page)

cortical cataracts and that these were of two types [3] bearing a constant relation to the source of dietary protein. Protein is the chief food requirement of the carnivorous urodele larvae. Details of the nutritional study have already been reported. In the present paper, after a description of the normal lens of Amblystoma and reference to literature concerning amphibian lenses, the two types of cataract nutritionally produced will be compared.

NORMAL LENS OF AMBLYSTOMA

Normal lenses have been found in all salamander larvae of the genus Amblystoma and of other genera collected by me from their native outdoor pools and in all larvae reared in the laboratory on raw muscle (beef, chicken, halibut) or raw liver (beef) or on a semisynthetic diet containing as chief ingredient a powdered preparation of one of these tissues. The lens is situated behind the iris, which is flat, not curved to the lens contour, as in Anura. More than a third of the lens protrudes through the pupil and can be observed quickly by the unaided eye or examined more thoroughly with a low powered lens. There are

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EXPLANATION OF FIGURE 1

A, a cataract caused by a diet with a high content of purified casein, showing the thin space between the opacity and the capsule and the nucleus unaffected (× 10). *B*, a normal lens by transmitted light (× 20). *C*, an early stage of a cataract due to a diet containing purified casein, showing striations between the equator and the anterior pole (× 20; from Patch [3b]). *D*, a late stage of shrinking, with the lens not visible and the pupil depressed (× 10). *E*, a subluxated lens (left eye) during shrinking, thirty-nine days after the maximum swelling, from a larva fed a diet of purified casein (× 10). *F*, the right eye of the last animal fifteen days later (× 10). *G*, the maximum swelling in the cataract of a larva fed a diet containing chicken myosin (× 20). *H*, the right eye of the last animal, showing unilateral subluxation (× 20). *I*, the black line in the outer cortex in the early stage of cataract of the second type (× 20). *J*, a black line buried by a thick layer of clear lens tissue after a period in which the larva was on a diet of raw beef liver (× 20; from Patch [3b]). *K*, the maximum swelling in the left lens of a larva with a cataract of type II, showing the wide, fluid-filled space between the cataract and the capsule, with the nucleus unaffected (× 20). *L*, a late stage in the lens shown in *K* (× 20). *M*, a late stage in the right lens of the same animal at the same time (× 20).

The magnification indicated in all the illustrations is approximate. The anterior poles of the sectioned lenses are at the left.

C and *J* are reproduced with the permission of the Wistar Institute of Anatomy and Biology, from the *Journal of Nutrition* (**22**:382 [Oct.] 1941).

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3. Patch, E. M.: (*a*) Cataracts in Amblystoma Tigrinum Larvae Fed Experimental Diets, Proc. Soc. Exper. Biol. & Med. **46**:205-207, 1941; (*b*) Dietary Production of Cataracts in Larval Amblystoma Tigrinum, J. Nutrition **22**:365-382, 1941.

no eyelids in Amphibia until late larval life. The normal lens appears black by reflected light and colorless and transparent by transmitted light (fig. 1 *B*). Sections of lenses from a young larva (fig. 2) and from an older one (fig. 3) show the increase of the lens index and the transfer of the fiber-forming cells of the epithelial border from their early posterior position to one in the equatorial zone.

Literature on the Normal Amphibian Lens.—A detailed survey of the literature on the normal amphibian eye was presented by Franz [4] in his comparative anatomy of vertebrate eyes. This account, suggested to me by Prof. George Wagner, of the Zoology Department of the University of Wisconsin, gave the chief facts from the best reports

Fig. 2.—A normal lens, nearly round, of a young larva, showing meridional row cells surrounding the posterior pole (× 65).

before 1934 concerning all parts of the eye in different vertebrates and included the most explanatory figures.

A series of accurate studies on the development and structure of the lens in different vertebrate classes and orders was made by Rabl. He called attention to the general interest of the amphibian eye (1898) due to its changes from the early form used in water to the later adaptation for use in air, a medium of different refractive index, and he

4. Franz, V.: Vergleichende Anatomie des Wirbeltierauges, in Bolk, L.; Göppert, E.; Kallius, E., and Lubosch, W.: Handbuch der vergleichenden Anatomie der Wirbeltiere, Berlin, Urban & Schwarzenberg, 1934, vol. 2, pt. 2, pp. 989-1292.

named the urodele eye the smallest in all gnathostome vertebrates. He found the amphibian lens to be less completely round than that of the lower vertebrate class of fishes, the equatorial diameter being largest and the posterior curvature being greater than that of the anterior surface. He described the sutures as linear, like those in later descriptions of the first human sutures [5] during the early spherical stage of

Fig. 3.—A normal eye of an advanced larva (× 45). The equatorial diameter is definitely greater than the axial, and the meridional row cells are near the equator. The width of the fibers is shown in the displaced portion. The lids are developing (Maggiore, 1912, cited by Franz [4]). The scleral cartilage characteristic of urodele larvae persists into adult life in one genus only, Amblystoma, according to Stadtmüller, 1914 (cited by Franz [4]).

5. Mann, I. C.: The Development of the Human Eye, London, Cambridge University Press, 1928.

the human lens. The amphibian sutures are placed like those of the selachian lens, however, the anterior being vertical and the posterior horizontal; they are shorter than the fish sutures and approximate one fourth of the equatorial diameter of the lens by Rabl's measurements. He found the lens epithelium of young urodele larvae to be of uniform thickness and to extend nearly to the posterior pole (fig. 2), with the border cells arranged in regular meridional rows, which retreat gradually during larval life to a position near the lens equator. The end cell of each meridional row forms new lens fibers, which are long, flattened cells, hexagonal or, sometimes, rectangular in cross section, with serrated longitudinal edges. Rabl reported that these cells lose their nuclei when the cell ends reach the sutures. The fibers are arranged in radial lamellas, with a number and order like those of the meridional rows, and form the chief substance of the lens.

Aid toward understanding the normal lens of Amphibia and its relations to other parts of the eye was obtained from the descriptions and pictures by Beer (1898) in his article on accommodation of the lens in that class, one of a series of papers on this process in the different classes and orders of vertebrates. His theory of lenticular accommodation in Amphibia was poor, however, because he was unaware of the double nature of the ciliary muscle (tensor choroideae, H. Virchow, 1885) and also of the presence of a protractor muscle (single in urodeles). Complete descriptions of the lens muscles were given later by Tretjakoff (1906) and by Okajima (1910), while Hess (1911) investigated the nature of the muscular action. Another aid toward understanding the normal amphibian lens was found in diagrams from one of Spemann's early works on the amphibian lens included in his review [6] of experimental studies on developing amphibians.

URODELE NUTRITION

In studying the influence of nutrition on larvae of the urodele genus Amblystoma, I early found that these animals are subject to different diseases like those of man and respond to like treatment.[7] After the embryonic yolk material has been completely utilized, the new environmental factor of food becomes the chief determining force. During larval

6. Spemann, H.: The Development of the Vertebrate Eye as an Example of a Composite Organ, in Embryonic Development and Induction, New Haven, Conn., Yale University Press, 1938, chap. 3.

7. Patch, E. M.: (*a*) Laboratory Controlled Development and Growth of Urodeles, to be published (work done [1926-1927] at the Osborn Zoological Laboratory of Yale University under the direction of Prof. R. G. Harrison); (*b*) Calcifying Factors in the Diet of Salamander Larvae, Science **81**:494-495, 1935; (*c*) Dietary Production and Prevention of Anemia in Larval Amblystoma, ibid. **83**:560-561, 1936.

growth and the gradual reconstruction in preparation for repeating the ancestral transfer from life in water to life on land, amphibians are especially sensitive to small variations in diet.

Nutrition of the Urodele Lens.—The lenticular environment is the same in Amphibia as in the higher vertebrates, including man. The lens is supported by the fine fibers of the zonule radiating from the ciliary body to the equatorial region of the lens; it meets the aqueous humor anteriorly and rests posteriorly on the vitreous body (Szent-Gyorgyi, 1914). The capsule is semipermeable, and inner channels of exchange exist between the serrated edges of the individual fibers. There is no direct blood supply to the amphibian lens at any time in its development, and the human lens has such a supply for only a short period of fetal life. Thus, the possible avenues of nutrition for the lens of Amblystoma and the lens of man are the same, as are also the method of lenticular formation and growth. Lenticular growth is continuous throughout life,[8] as is characteristic of ectodermal derivatives in general. Growth is accompanied by a high susceptibility to disease. The particular susceptibility of the amphibian lens, with its unique structural history of change after feeding has begun, is not surprising and offers an excellent opportunity for study of lenticular health.

CATARACTS OF TYPE I

Cataracts of the first type appeared, as recorded, in larvae of Amblystoma tigrinum which had been fed the diet containing purified casein (fig. 1 *A, C, D, E* and *F*) and in 51 per cent of those fed seven diets each containing as chief ingredient one of the four most abundant proteins of muscle. Powdered preparations were made of myosin, globulin x, myogen and the residue (chiefly stroma protein) from the white muscle of chicken and of the first two and the last of these from beef muscle. Swelling and whitening of the lens in a larva fed a diet of chicken myosin (fig. 1 *G*) was accompanied by unilateral subluxation (fig. 1 *H*). Addition of the cystine supplement, which was an effective preventive with the diet of purified casein, did not have that action with the muscle protein diets, although twice the amount of cystine was effective with two of these diets. The amount of cystine needed by the lens probably varies widely according to the presence of other substances with which it reacts. Some of the cataractous larvae reared on the diet of beef residue metamorphosed to the adult form, in con-

8. (*a*) Clapp, C. A.: Cataract: Its Etiology and Treatment, Philadelphia, Lea & Febiger, 1934. (*b*) Krause, A. C.: The Chemistry of the Lens, in The Biochemistry of the Eye, Baltimore, Johns Hopkins Press, 1934, chap. 8. (*c*) Bourne, M. C.: Metabolic Factors in Cataract Production, Physiol. Rev. **17**: 1-27, 1937. Mann.[5]

trast to the anemic larvae of groups fed other muscle protein diets and fed the purified casein diet. This showed that the disease was specific, and the cystine was specific in action, not reducing the anemia.

In cataracts of the first type which have been studied histologically, the first indication of lenticular disturbance has been the breakdown of the membranes between the cells of the meridional rows with change in shape, size and position of the degenerating nuclei. Occasional granulocytes have been visible near the lens surface. Rows of vacuoles appearing like filamentous algae [9] between the outer fibers (fig. 4) have pushed them apart, and proliferation of the anterior epithelium has

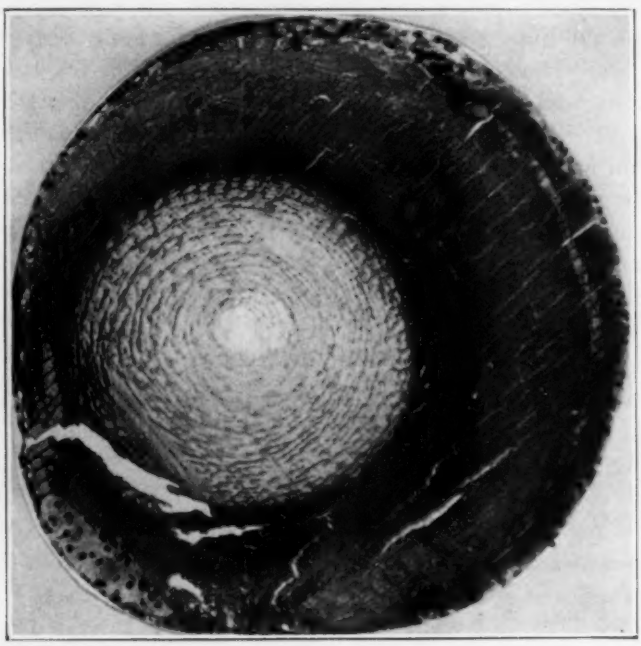

Fig. 4.—Section of an early cataract due to a diet of stroma protein from beef muscle, showing epithelial degeneration and proliferation, vacuoles in rows like filamentous algae in the outer cortex and the inner cortex unaffected (× 90).

occurred. Breaks of the capsule found in the sections may have been the cause or the effect of the disease or may have been made during preparation of the slides. Gradually the entire cortex of the lens has assumed a vesicular appearance (fig. 5), first with fine granular contents and later clear. Scattered vacuoles containing debris of various sorts have appeared near the lens surface. Liquefaction has followed, until

9. Fuchs, E.: Diseases of the Eye, 15th German edition translated by E. V. L. Brown, English ed. 10, Philadelphia, J. B. Lippincott Company, 1933.

the entire cortex has become a shapeless accumulation of mucin-like strands with phagocytes and various cortical remnants (fig. 6). In the late stage pictured here, dislocation of the undisturbed nucleus and the surrounding cortical debris into the anterior chamber occurred, possibly during preparation of the sections. No nuclear degeneration

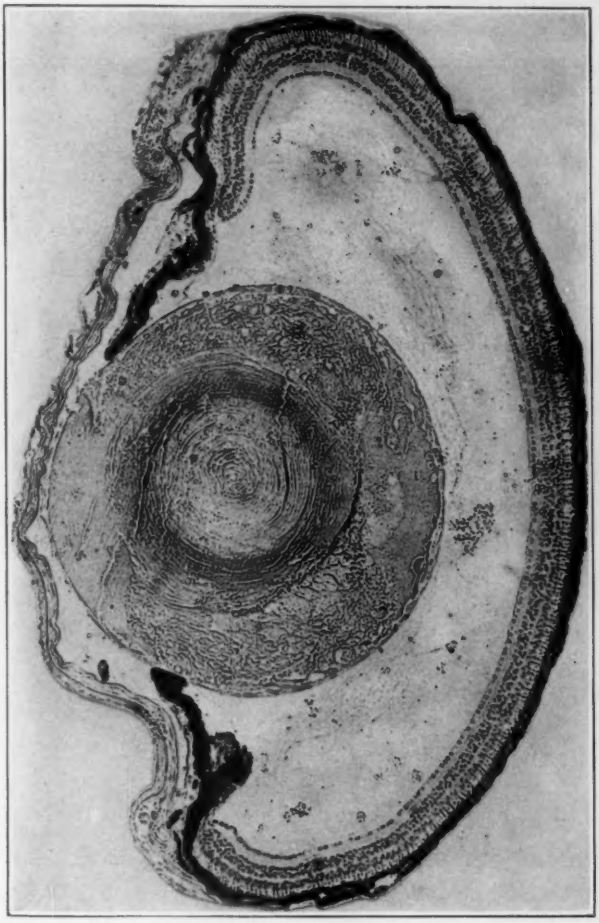

Fig. 5.—The maximum swelling in a cataract due to a diet of purified casein, showing vacuolation and vesiculation of the cortex, with the nucleus unaffected (× 60).

has been found in the lenses sectioned, but this change is suggested by the small size of the lens in the second picture of subluxation in a larva on a casein diet. The cataracts were all bilateral, but there was sometimes whitening of the lens in one eye as long as six months before it was seen in the other eye.

CATARACTS OF TYPE II

In contrast to cataracts of the first type seen in the larvae of Amblystoma tigrinum, cataracts of type II are always visible in an early stage, appearing as a fine line in the outer cortical layer of the lens parallel to its surface (fig. 1 *I*) and surrounded by transparent lens tissue. Often there has been a long period with no apparent change

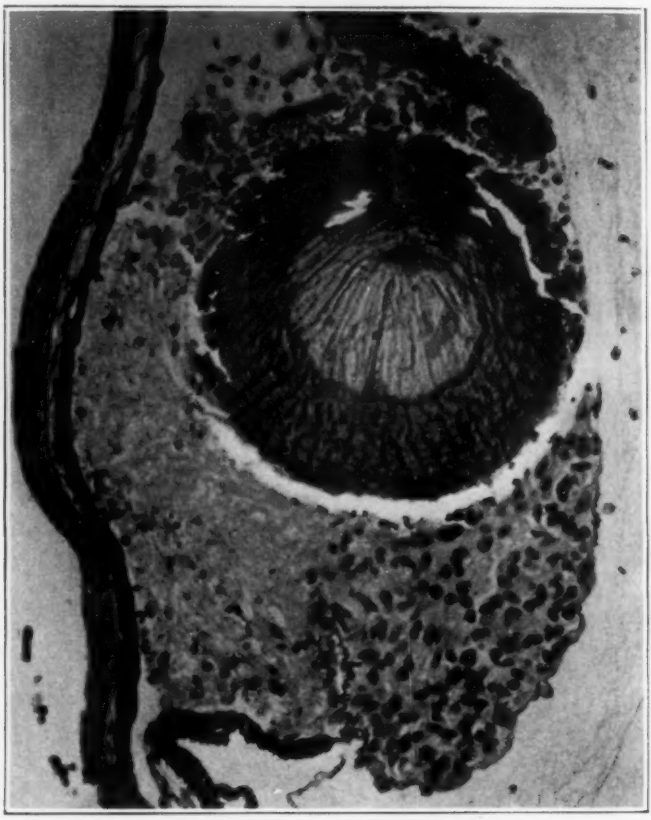

Fig. 6.—A late stage of cataract due to a diet of stroma protein from beef muscle, showing cortical debris and proliferated epithelial cells, with the nucleus unaffected (× 120).

except, occasionally, broadening or duplication of the line. If the faulty diet was replaced during this period by a diet forming normal lens tissue, the dark line became buried by a widening band of clear lens fibers (fig. 1 *J*), but the line never disappeared. If the faulty diet was continued until whitening of the cortex occurred, during this change the dark line disappeared and there was a marked accumulation of viscous liquid between the opacity and the lens capsule (fig. 1 *K*).

Subsequent changes in this type of cataract have been small and slow (fig. 1 *L* and *M*), with little loss in size and hence no lenticular migration. No subluxation has appeared with cataracts of this type, and bilateral differences in the beginning time and in the rate of progress have been less than in the other type of lenticular disease.

Except for the protein-containing parts, diets causing the two types of cataract have been alike. The dark line was seen in the lenses of

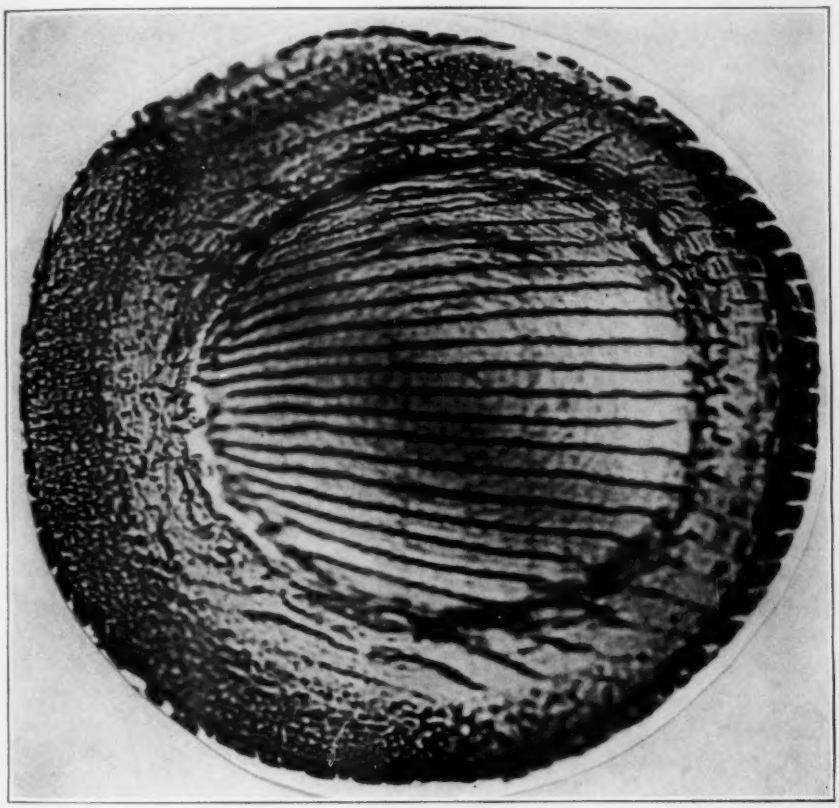

Fig. 7.—Section of a cataract of type II during early cortical changes, showing anterior granulation and the epithelial cells in the normal position (× 220). The section is lateral to the center of the lens, through the meridional row cells.

larvae which had been fed for about a month on diets whose protein was supplied by powdered whole blood (beef or turtle), defibrinated blood, hemoglobin or globin. Prevention was not attained by supplementary use of cystine alone, even in high amounts, but a combination of this acid with the other two components of glutathione was more effective in lowering the frequency and the intensity of the dark line than the other two components without cystine. Although cystine

supplementation gave the same amino acid combination as the diet of purified casein without the cystine, cataracts of the first type did not appear. Clearly, an important causal factor was not detected. In general, the growth and the development of the larvae fed the blood diets were poor, and they were not improved by the amino acid supplements. No statement can be made concerning specificity of ocular disease of this type. It is not known whether the cortical whitening,

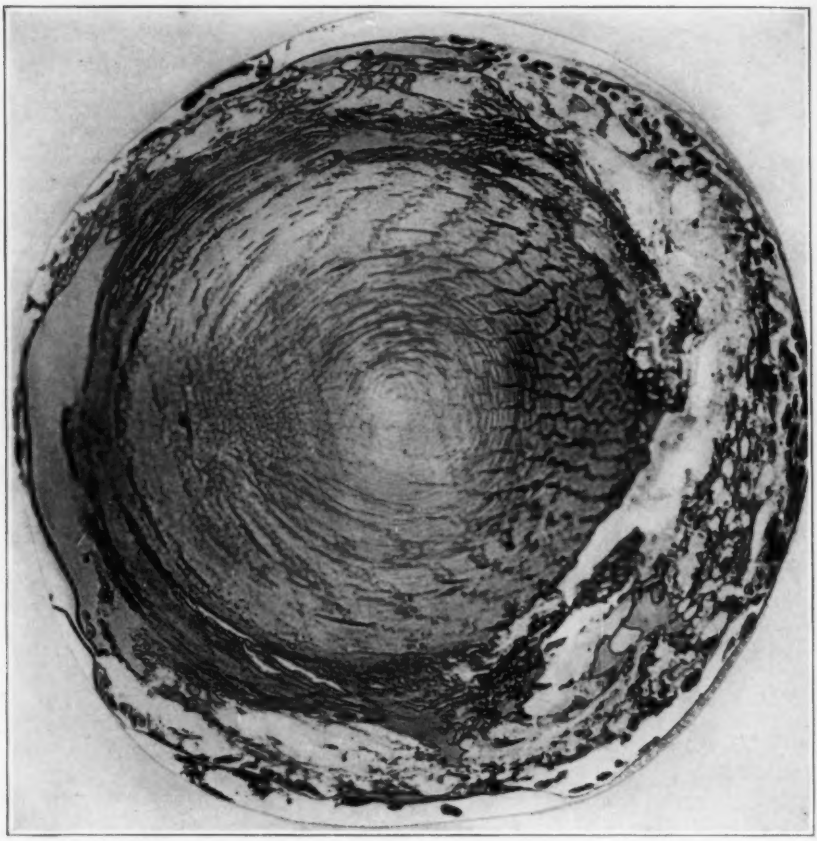

Fig. 8.—The maximum swelling in a cataract of type II, showing the epithelium disarranged (× 190). There are no vacuoles or vesicles, as were seen in type I.

occurring in 37 per cent of the larvae showing the early lenticular line, was due to a recurrence of the original disturbance at a heightened intensity or to a new abnormality of conditions.

In histologic sections made of lenses with the dark line, it has appeared only as a separation of the outer rim of the lens. Absence of a band in cleared but unstained sections prepared from lenses fixed

in solution of formaldehyde or in 95 per cent alcohol suggests that the band was not a black deposit of foreign material but a zone of faulty fiber formation or of disintegration causing a refraction of the light rays. The first histologic change seen in this type of cataract has been a coarse granulation at the anterior ends of the outer fibers (fig. 7) spreading through them longitudinally and inward to the next fiber layer. With extension of this process, clear homogeneous regions have appeared (fig. 8). In the stage of greatest swelling there has been seen the first evidence of epithelial degeneration, beginning in the meridional row cells. The vacuoles and vesicles characteristic of the first type of cataract, as also the extensive liquefaction and decrease in size seen there, have not been found in cataracts of the second type.

The black line formation resembles descriptions of the early stage of zonular cataract in children,[10] a disease considered due to faulty nutrition. In contrast, salamanders with the banded lenses have shown no rickets or tetany, which are associated with zonular cataract, although poor muscular tone and faulty calcification have been produced in salamander larvae by other diets.[11] Apparently the dietary condition affecting the lens is of a borderline nature, at times causing poor lens fiber formation and at times not being great enough to influence the process, and does not affect the epithelium until the cortical change has spread.

COMMENT

The cataracts which appeared in the salamander larvae formed in the more recent cortical portion of the lens, the portion made after introduction of the faulty diet. The disease varied with the source of dietary protein, the largest component of each diet given to these carnivorous animals. Whether the disease was related only to the protein composition of the diet or partly to some associated substance is not known. The vitamin supplements were alike for all diets being compared for effect of the protein sources. The carbohydrate in all the rations was cooked corn starch, except for the ration of purified casein and powdered milk, which contained 7 per cent of galactose in the sugar of the milk. Cataracts of the same type produced by this diet were caused by other diets without this sugar. Fat variations were ineffective in changing the occurrence of the disease, as were mineral supplements of different combinations.

The nonrelation of dietary supplementation with minerals to production of the lenticular disease suggests a true difference between the cause of the cataracts in the salamander larvae and the cause of

10. Kirby, D. B.: Diseases of the Crystalline Lens, in Berens, C.: The Eye and Its Diseases, Philadelphia, W. B. Saunders Company, 1936, chap. 37. Fuchs.[9] May.[2]

11. Patch (footnote 7 *a* and *b*).

the cataracts which developed in frogs and in several forms of mammals in the middle of the last century. Kunde [12] stated the belief that the cataracts appearing in frogs and in cats which he had given a solution of sodium chloride by mouth, by anus or by subcutaneous injection were due chiefly to withdrawal of water. This theory was disproved by Mitchell,[13] who assigned to osmotic changes the cataracts developing in frogs after he had injected a syrup of sugar into their dorsal subcutaneous sacs. He suggested a like explanation for the occurrence of the lenticular disease in diabetic patients affected by small amounts of sugar given over long periods of time. More recently, Lebensohn [14] pointed out that the cataracts due to galactose feeding are not of true nutritional nature. Bellows and Chinn [15] reported a cataractogenic action of a number of salts, sugars and other substances when injected in dissolved form into dogs. They reviewed the literature and discussed the possible significance of osmotic derangement in the pathogenesis of cataract.

The preventive action of cystine, the amino acid which is a characteristic component of ectodermal structures, is not surprising in view of the origin of the lens. The same statement holds true of the other amino acids combined with cysteine (the reduced form of cystine) in glutathione, the regulatory tripeptide found in all active plant and animal tissues [16] and present in the lens most abundantly where new fibers are being formed.[8b] Possibly it is in action as a constituent of this compound that cystine has been protective for mammals against cataracts due to toxins,[17] to deficiency of the riboflavin component of vitamin G [18] and to the action of galactose.[19] There has been controversy about the relation of glutathione to tissue respiration.

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12. Kunde, F.: Ueber Wasserentziehung und Bildung vorübergehende Katarakte, Ztschr. f. wissensch. Zool. **8**:466-486, 1857.

13. Mitchell, S. W.: On the Production of Cataracts in Frogs by the Administration of Sugar, Am. J. M. Sc. **39**:106-110, 1860.

14. Lebensohn, J. E.: Biochemistry of the Lens: A Résumé, Am. J. Ophth. **23**:784-792, 1940.

15. Bellows, J. G., and Chinn, H.: Biochemistry of the Lens: XIII. Production of Lens Opacities by Injection of Hypertonic Solutions, Arch. Ophth. **25**: 796-810 (May) 1941.

16. Sherman, H. C.: Chemistry of Food and Nutrition, ed. 6, New York, The Macmillan Company, 1941.

17. Bourne, M. C., and Young, L.: The Metabolism of Naphthalene in Rabbits, Biochem. J. **28**:803-808, 1934.

18. Bourne, M. C., and Pyke, M. A.: The Occurrence of Cataract in Rats Fed on Diets Deficient in Vitamin B_2, Biochem. J. **29**:1865-1871, 1935.

19. Bellows, J. G.: Biochemistry of the Lens: IX. Influence of Vitamin C and Sulfhydryls on the Production of Galactose Cataract, Arch. Ophth. **16**:762-769 (Nov.) 1936. Yudkin, A. M., and Geer, H. A.: An Investigation of Experimental Cataracts in the Albino Rat: Clinical Implications, ibid. **23**:28-40 (Jan.) 1940.

Judged by gross and histologic aspects, two types of cataract were produced in the salamander larvae. Grossly, they differed in visibility of an early stage, in rate of progress, in amount of liquid between the capsule and the whitened cortex and in the late changes. Histologically, they were seen to differ in the initial locus of attack as well as in the method and the extent of progress. It appeared as if more water had been taken into the lens in the first type of change, causing more hydrolysis, more degeneration, increased osmosis, swelling and, finally, more decrease in size of the lens as a whole. In the second type the diseased lens had a drier appearance, as if little of the water entering through the capsule had penetrated the lens. There are statements in the literature that less water enters slowly developing cataracts.[8b] Study of preserved cataracts in more stages and the making of slit lamp observations might show whether the two types of cataract are related and how similar they are to the types of lenticular change in human beings.

The function of the lens is physical rather than physiologic,[8a] and the lens requires much less food for energy production than for fiber formation. The presence of the various amino acids essential for normal fiber structure is necessary to support the action of glutathione. Other directive substances may function in the healthy lens, possibly some of them being vitamins or other food components not yet identified. Bellows and Chinn,[20] recently reviewing theories of cataract, stated that no one theory is adequate, that usually several causes are active together, that animal experimentation is probably the best approach to the problem and that a solution may be favored by recent biochemical advances, especially in the field of protein structure and of intracellular respiratory enzymes.

The cataracts produced in the salamander larvae were clearly due to nutrition, and any finding of cause depends on nutritional studies. The solution of such problems is often elusive, particularly when directly sought, and may come from least expected sources. The ease of producing and observing lenticular disease in these small amphibians, its apparent similarity to human cataract, and the other parallelisms between disease and health in these animals and in man suggest that they might aid in the detection of general factors acting in production of cataract.

SUMMARY

Two types of cortical cataract have been produced in larvae of the tiger salamander, Amblystoma tigrinum, with a definite and constant relation to the source of dietary protein, the chief food requirement of

20. Bellows, J. G., and Chinn, H.: Theories of Cataract, Arch. Ophth. **26**: 1066-1093 (Dec.) 1941.

the carnivorous urodeles. The gross and histologic differences between the two types are described and also the apparent gross similarities to human cataracts. The nature of the amphibian lens is outlined and the reasons for its high susceptibility to dietary irregularities. The problem is complex and requires a nutritional approach, but its study may aid in detection of some of the general causes of cataract.

The experiments and reading reported in this paper were done at the University of Wisconsin. The first cataracts were observed during study in the zoology department. In 1934 repetition of the experiments was carried on in the anatomy department of the medical school, where roentgenologic studies of calcification were being made. The last part of the work was done in the physiology department. The photographic work was done in the anatomy department under the direction and with the aid of Prof. H. W. Mossman.

FUNDUS OCULI IN HYPERTENSIVE VASCULAR DISEASE

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During the past years many investigations and clinical studies have been made for the purpose of determining the primary causative factor of hypertensive vascular disease, or essential hypertension, but this factor has not as yet been established.

Hypertensive vascular disease is considered a clinical entity. It is extremely prevalent and in its terminal stages is liable to produce disastrous involvement of the vital organs. Its cardinal symptom is persistent high blood pressure.

Two forms of hypertensive disease are considered in this paper: essential benign hypertension and malignant hypertension. This classification is not accepted by all internists, but since it is in general use it will be employed here.

Essential benign hypertension (benign nephrosclerosis) occurs generally in middle-aged persons with persistent high blood pressure. The subjective symptoms are of a mild and chronic nature. The patient is apparently in good health and may live for many years. The vision frequently is normal, as are the fundi, although there may be slight fundus changes resembling those in retinal arteriosclerosis. In the course of benign hypertension the patient may die of a thrombus, a hemorrhage or softening of tissue in one of the vital organs. These serious associated lesions should not affect the use of the term "benign" in describing this form of hypertension.

Malignant hypertension (malignant nephrosclerosis), or necrotizing arteriolitis, occurs in younger persons than the benign form, but rarely in children. This disease is a serious one with an acute onset. Visual disturbances and fundus lesions are usually early manifestations. The blood pressure, especially the diastolic, is pronouncedly elevated. Headaches are persistent and excruciating. In some cases death occurs a few weeks or months after the onset of the disease, while in other cases the patient may live for seven or eight years. Use of the term "malignant hypertension" is warranted, however, in describing the latter cases.

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From the Department of Ophthalmology of the New York Post-Graduate Medical School and Hospital (Columbia University).

A similar problem arises with cancer, to which the term "malignant" is applied though the duration of life after recognition of the lesion may be a matter of years.

Many authorities consider malignant hypertension a clinical entity, some consider it a superadded condition, while others believe that it is the fulmination of benign hypertension. To illustrate the last-mentioned contention, a case is briefly reported, with the permission of Dr. Herbert J. Wiener.

History and Examination.—N. L., a white man aged 36, was first seen by Dr. Wiener in January 1927 because of albuminuria discovered at a life insurance examination. Physical examination showed his condition to be normal except for a slight enlargement of the heart to the left and hyperreflexia. The blood pressure was 150 systolic and 85 diastolic. The urine showed a heavy trace of albumin and an occasional hyaline cast, with a specific gravity of 1.024. The blood chemistry was entirely normal.

Course.—The patient was seen at intervals of a few months during the next seven years, and no material change in his condition was noted. His symptoms during this period were chiefly referable to autonomic imbalance, comprising insomnia and moderate digestive disturbances. At the end of seven years, on Feb. 1, 1934, his blood pressure was 160 systolic and 92 diastolic, and from this date he began to be troubled by increasing late afternoon and nocturnal headaches. A few red blood cells and fine granular casts appeared in the urine. During the next four years the blood pressure rose progressively, and in October 1938 it was 243 systolic and 148 diastolic. He was admitted to the Post-Graduate Hospital on October 4 and examined by me on the following day. A diagnosis of benign hypertensive retinopathy was made (*A* in the accompanying figure).

Polyuria had been established, with a falling specific gravity but with an increase in the amount of albumin; there were no pus cells in the urine at any time. The blood chemistry remained entirely normal except for a slightly increased uric acid content (4.1 mg. per hundred cubic centimeters). There were occasional mild symptoms of hypertensive encephalopathy.

On account of the progressively mounting blood pressure and the persisting and excruciating frontal headaches, an omentonephropexy on the right side was performed at the New York Post-Graduate Hospital, by Dr. Franklin Carter, on October 20. The patient left the hospital on November 15, with no improvement in his condition.

He was readmitted to the hospital on March 19, 1939. Three days later the urea nitrogen content was 26 mg. per hundred cubic centimeters, and, after consultation, the operation was repeated on the left side on April 3. Two days later the urea nitrogen content mounted to 47 mg., and one day before death it rose to 84 mg. Death occurred on April 21, with terminal symptoms of uremia. The operative procedure employed is no longer performed at the Post-Graduate Hospital, having been superseded by the Smithwick operation.

Pathologic Report on the Kidney Tissue (Dr. Arthur C. Allen).—Section of Right Kidney: This section was a fragment of renal tissue measuring 7 by 5 mm. The glomeruli presented early stages of sclerotic thickening of their basement membranes. No necrosis was found within them. Bowman's capsules were, with rare exception, only slightly or not at all thickened. The tubules contained a moderate amount of protein precipitates and desquamated epithelial cells. A few

small foci of interstitial fibrosis with tubular atrophy were present. The walls of the interlobular arteries and of the afferent arterioles were distinctly thickened and their lumens narrowed by homogeneously hyalinized material. No evidence of necrosis or of increased internal cellularity of the vessels was observed in this small section. Reduplication of the elastica was observed in the interlobular and arciform arteries. The diagnosis was arteriosclerosis of the kidney (benign nephrosclerosis; *B* in the figure). It is obvious, however, that this small section was not necessarily representative of the entire kidney.

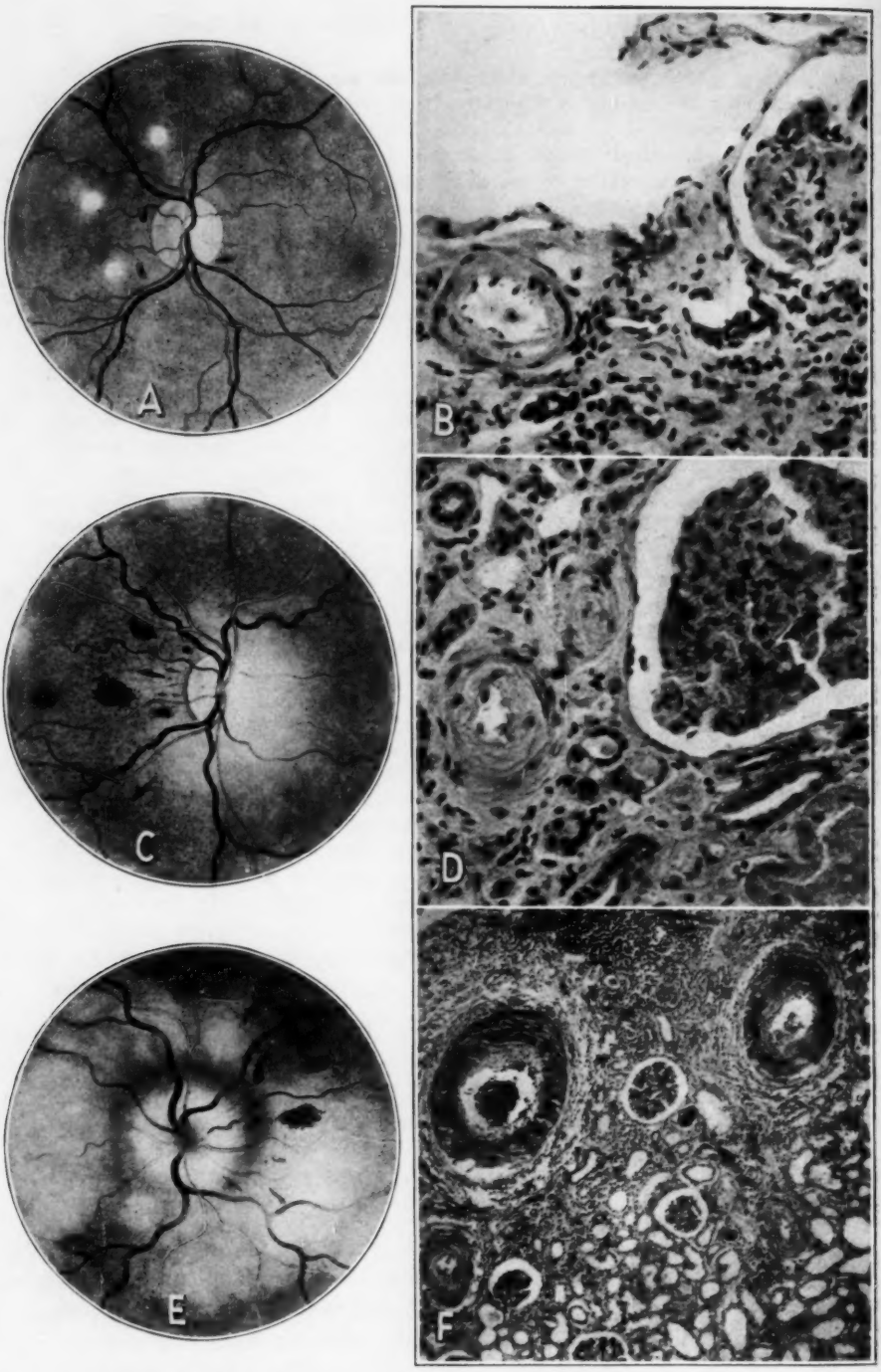
Section of Left Kidney: This section of renal tissue, measuring 6 by 5 mm., showed more advanced sclerosis of the basement membranes of the glomerular capillaries than the preceding one. Many of the glomeruli were partially or completely sclerosed, with corresponding thickening of Bowman's capsules. No glomerular necrosis was visible. The tubules contained protein and precipitates and desquamated epithelial cells. The tubular atrophy and interstitial fibrosis were considerably more extensive in this section than in one taken five months before. The interlobular arteries and afferent arterioles presented a profound hyaline thickening of their walls and narrowing of their lumens. The intima of several of the interlobular arteries manifested an increased cellularity, and red corpuscles were present in their walls, as in the vessels in cases of accelerated or malignant nephrosclerosis. Red blood cells were visible also in the walls of the afferent arterioles. In addition, these vessels presented fibrillation, granularity and fine vacuolization (probably fat) of the hyalin of their walls. Distinct reduplication of the elastica was observed in the interlobular and arciform arteries. The diagnosis was severe arteriosclerosis of the kidney, suggestive of the accelerated, or malignant, phase of nephrosclerosis (*D* in the figure).

Ocular Findings.—On the patient's admission, several ocular examinations revealed pronounced and progressive fundus lesions of both eyes, characteristic of the moderate form of malignant hypertension (*C* in the figure). A week after the second operation the fundi showed papilledema, engorged and tortuous retinal veins, attenuated arterioles, extensive retinal edema obstructing the visibility of the arterioles in the greater portion of the fundus, numerous woolly exudates around the disk and striate and circular hemorrhages. In other words, the fundi presented the picture associated with the severe form of malignant hypertension (*E* in the figure), a change from the benign picture seen five months before, at the time of first admission.

From the point of view of diagnosis and prognosis, this case illustrates the value of ophthalmoscopic examination, because the fundus lesions typical of the malignant phase were discovered shortly before there was evidence of malignant renal insufficiency, i. e., nitrogen retention, etc.

Hypertensive disease is produced primarily by a disturbance of the walls of the arterioles of the entire body and especially of the eye, heart, brain and kidneys. The retinal arteriolar lesion is considered to be due primarily to an angiospasm, possibly of vasomotor origin, which contracts the arterioles as in toxemia of pregnancy or in pyelonephritis. The latter condition is illustrated by the following case:

A woman aged 26 suffered from unilateral pyelonephritis associated with bilateral severe fundus lesions, angiospasm of the retinal arterioles and secondary hypertension with a blood pressure of 180 systolic and 130 diastolic. Intermittent exami-



A, benign hypertensive retinopathy. *B*, benign nephrosclerosis. *C*, malignant hypertensive neuroretinopathy. *D*, malignant nephrosclerosis. *E*, malignant hypertensive retinopathy with papilledema (severe form). *F*, malignant nephrosclerosis in pyelonephritis.

nation of the urine revealed innumerable pus cells and the presence of Bacillus coli. No retention of nitrogen was reported. After a nephrectomy performed by Dr. Joseph Hyams on Oct. 3, 1941 at Post-Graduate Hospital, the systemic hypertension was reduced to 164 systolic and 90 diastolic and the fundus lesions were resorbed, leaving no trace. Diagnosis of the renal condition was as follows: suppurative pyelonephritis, periarteritis nodosa and severe renal arteriolar sclerosis of the malignant type (*F* in the figure). The patient was discharged on October 23 and went to Johnstown, N. Y. Her physician wired me in April 1942 that after she had been well for several months, the blood pressure went to 270 systolic and 200 diastolic, blindness developed and she died, on February 14, of cerebral hemorrhage and heart failure.

The followng changes in the fundus vasculature may take place: Diffuse arteriolar sclerosis may develop if the angiospasm is not alleviated by treatment. The ocular circulatory disturbance first affects the endothelial lining of the arterioles, causing their degeneration and proliferation, with encroachment on their lumens. The internal elastic lamina becomes reduplicated and split, and the intima and media become hypertrophied. Degeneration of the vascular walls and, finally, necrosis may develop. These changes result in contraction of the arterioles and often endarteritis, as a consequence of which the lumens of the vessels frequently become blocked, producing ischemia of the surrounding tissue, with edema, hemorrhages and exudates. The retinal venules are dilated and at times show local areas of hyperplasia. In malignant hypertension the outstanding lesion is necrotizing arteriolitis.

The fundus lesions may be progressive, stationary, retrogressive, or remittent; repeated examinations during the course of the disease will establish their status. The internist's clinical diagnosis of benign or malignant hypertension should accompany the ocular findings in order to establish a correlation, because, while the ocular vascular sclerosis is often a clinical index of the generalized arteriolar sclerosis, conditions other than hypertension—arteriosclerosis, cerebral tumors, etc.—may affect the eyegrounds and produce a fundus picture simulating that of benign or malignant hypertensive disease. The lesion in hypertensive disease is due basically to a degenerative, not an inflammatory, process; accordingly, the term "retinopathy" is applied to the retinal lesions.

Examination of the fundus should be performed by means of the electric hand ophthalmoscope with good illumination. The pupils should be fully dilated with a 4 per cent solution of cocaine hydrochloride, since a wide pupil permits a more thorough examination. The physician should be acquainted with physiologic variations and also with refractive errors, the latter being overcome by corrective lenses in the ophthalmoscope. The fundus camera is a useful instrument for studying and recording the lesions at various periods during the disease.

HYPERTENSIVE DISEASE AS IT AFFECTS THE FUNDUS

I have adopted the following classification in diagnosing hypertensive disease as it affects the fundus:

Essential Benign Hypertension.—The papilla may be somewhat hyperemic, with its margins sharply outlined. The arterioles frequently are contracted and tortuous, and their lumens show a prominence of their central light reflex. The venules are slightly dilated and congested, and where they are crossed by sclerosed arterioles they are compressed and deflected. This change occurs mainly on the superior or inferior temporal vein. A few hemorrhages or glistening whitish plaques may appear near the posterior pole of the eye. The changes are few and slight; as previously mentioned, the fundus may appear normal or the picture may resemble that seen in arteriosclerosis. The diagnosis based on the fundus changes may be benign hypertensive retinopathy or benign hypertensive retinal arteriolar sclerosis.

Malignant Hypertension.—The fundus shows characteristic early and late manifestations. These changes are diversified, comprising moderate and severe lesions of arteriolar sclerosis, hemorrhages, exudates and edema. They are located mainly at or near the posterior pole of the eye. The fundus lesions are classified as follows:

Moderate Form: The arterioles are contracted, their central light reflex is prominent and they pursue a tortuous course. There is moderate venous hyperemia, with compression and deflection of the veins where they are crossed by sclerosed arterioles; moderate edema of the disk and surrounding areas; numerous hemorrhages, small and large; white lines bordering the arterioles and venules; beading of the arterioles and at times silver wire vessels, and rarely a partial star figure in the macular area. The diagnosis based on the fundus picture may be malignant hypertensive neuroretinopathy or malignant hypertensive retinopathy.

Severe Form: There is a progression of the moderate lesions associated with pronounced papilledema or choked disk, large edematous areas in the perimacular region and occasionally a complete star figure in the macula. Some arterioles appear as white cords, owing to endarteritis. Detachment of the retina and choroid, hemorrhages into the vitreous and pigment spots are rarely present. The severe form signifies the terminal phase of malignant hypertension. The diagnosis based on the fundus picture may be malignant hypertensive retinopathy with papilledema.

Hypertensive disease is frequently associated with chronic glomerular nephritis, toxemia of pregnancy, diabetes, arteriosclerosis and pyelonephritis. The signs in the fundus of benign or malignant hypertension may accompany the fundus lesions associated with these dis-

eases. If a patient is seen for the first time during the late stages of one of these diseases, unless a previous history is obtained it is impossible to judge from the eyegrounds which is the prevailing disease or in what order the changes occurred. In cases of toxemia of pregnancy and of pyelonephritis, the toxic factors causing angiospastic contraction with fundus lesions and hypertension cause characteristic fundus changes.

COMMENT

Fundus lesions are classified and correlated with hypertensive vascular disease.

A diagnosis of general hypertensive vascular disease is essential to the interpretation of fundus lesions.

It is difficult to define the transition of fundus lesions from one form into another; the progression of these lesions will determine the classification.

The indication for operative procedures for the reduction of hypertension rests on the clinical symptoms and not on the ophthalmoscopic findings.

A terminal phase of malignant hypertension is recognized by papilledema, or swelling of the disk with an elevation of 2 or more D., in contradistinction to optic neuritis, in which there is but a slight elevation of the disk and surrounding tissue.

The prognosis for life in hypertensive vascular disease depends mainly on the involvement of the vital organs and not on the ophthalmoscopic findings.

An ophthalmoscopic examination is an invaluable aid in the diagnosis and prognosis of hypertensive vascular disease, as it provides a visible guide to the condition of the general vasculature such as cannot be observed in any other organ or tissue of the body.

29 East Sixty-Fourth Street.

BILATERAL THROMBOSIS OF POSTERIOR CALCARINE ARTERIES WITH SPARING OF MACULAR VISION

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Vascular accidents affecting the eye and the visual pathways are not uncommon, and the sequelae vary according to the extent and the site of the lesion. The ocular changes may be but a small part of an extensive lesion causing gross disturbances of motor and of sensory function. One may have paralysis of conjugate deviation, oculomotor palsies or complete or incomplete homonymous defects in the visual fields. Frequently the lesion can be located with anatomic precision but without much benefit to the patient.

Hemianopsia of vascular origin is usually sudden in onset and is caused by an embolus, thrombosis or rupture of a vessel supplying the optic pathways or the visual cortex. Such defects are fairly common and unless complete frequently pass unnoticed and are only discovered on a routine examination of the visual fields. The occurrence of bilateral hemianopsia with sparing of the macular field is, however, rather rare.

Bilateral hemianopsia is of vascular or of traumatic origin. Most of the traumatic cases were reported by English, French and German authors after the first World War, and the condition was caused by shrapnel or gunshot wounds of the occiput. Birth trauma [1] must be considered when bilateral hemianopsia is found in a young person with no other apparent history of trauma. In vascular lesions of the occipital lobe the fixation area is usually spared, and the spared area may extend upward or downward along the vertical meridian.[2] There is occasionally some improvement in the visual fields in the case of vascular lesions, while in the case of traumatic lesions improvement is rare and the fixation area is frequently involved.

The case of bilateral hemianopsia to be reported is one of the rarer cases in which no other neurologic or visual symptoms were noted apart from the inability to see first to the right and then, at a later date, also

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1. Pallarès, J.: Un cas d'hémianopsie double avec conservation de la vision maculaire après la naissance, Ann. d'ocul. **168**:45, 1931.

2. Traquair, H. M.: Clinical Perimetry, St. Louis, C. V. Mosby Company, 1940.

to the left. I was able to find only 1 other case reported in this country, and that was by Dunn [3] in 1895. No doubt there are other cases which have not been reported.

The patient, J. M., a man aged 49 years, was first seen on Sept. 26, 1941, complaining of inability to see to get around. He stated that on September 24 while talking to a neighbor he went completely blind for a few seconds; when his vision cleared up he had the feeling that he was looking through a narrow pipe. He consulted his local ophthalmologist, Dr. C. E. Gardiner, of Lebanon, Pa., who referred him for consultation.

The patient stated that he had always enjoyed good health until January 1940. At that time he had an attack of shortness of breath and of pain situated over his heart and radiating down his left arm. A few days later he noticed that he could not see things to his right. He was told that a clot of blood in his brain had destroyed his right fields of vision. He returned to his work in a candy factory and had no difficulty operating his machine. He has not had any difficulty in reading, except that for the past year or so he has had to hold the print farther away.

At no time has the patient had any speech difficulty, even at the time of loss of the right fields of vision. Both he and his wife denied that he had had any symptoms or signs suggestive of spatial disorientation or of any functional disturbance.

The patient was hospitalized for study. The impression of the cardiologist who saw him was that he had had a coronary occlusion associated with hypertension (blood pressure, 150 systolic and 110 diastolic) and arteriosclerosis. Neurologic examination revealed no mental abnormalities; the gait and station were normal, the posture was symmetric and the cranial nerves were normal. The face, tongue, and palate were symmetric. There were no sensory disturbances; pain, vibration and position sense were normal. There was no muscular atrophy, and muscular power was normal. The reflexes were hyperactive but equal; none was abnormal.

Laboratory studies, including a complete blood count, urinalysis, a Wassermann test of the blood and determination of the blood sugar, all gave normal results. On lumbar puncture the initial pressure was 190 mm. of water, the fluid was clear, the total protein content was 50 mg. per hundred cubic centimeters and the Wassermann reaction and the colloidal gold curves were normal. A stereoscopic roentgenogram of the skull did not reveal any signs of increased intracranial pressure. The conclusions were that no pathologic changes were present in the skull or in the sella turcica.

Ophthalmoscopic examination revealed the lids and the lacrimal passages to be normal. The conjunctiva and the sclera were clear; the corneas were clear and sensation to cotton wool was normal. The pupils were round, regular and equal and reacted promptly to light and in accommodation. The external ocular movements were full; convergence, however, was poorly performed. Ophthalmoscopic examination gave entirely negative results but for the vascular changes associated with a grade 1 hypertension. Slit lamp examination of the anterior segments did not reveal any changes. Visual acuity was 6/9 in the right eye, corrected to 6/6 with -0.25 D. sph. $\bigcirc$ -0.50 D. cyl., axis 90, and 6/9 in the left eye, corrected to 6/6 with -0.25 D. cyl., axis 180. With $+1.25$ D. sph. before each eye the patient could read Jaeger type 1 at 20 cm.

3. Dunn, T. D.: Double Hemiplegia with Double Hemianopsia and Loss of Geographical Centre, University M. Mag. **7**:578, 1895.

The visual fields are shown in figure 1; subsequent examinations disclosed no change. The patient read incorrectly plates 3 and 5 of the Ishihara test for color vision. He had first, second and third degree fusion as tested on the synoptophore. Optokinetic nystagmus was readily elicited upward, downward and on lateral motion, right or left.

After a review of the patient's history and visual changes it was concluded that the right homonymous hemianopsia, following his coronary attack, was probably caused by an embolus lodging in the left posterior calcarine artery. Unfortunately, visual fields were not taken at this time. The left homonymous hemianopsia was probably caused by a thrombosis of the right posterior calcarine vessel. The final diagnosis was bilateral occlusion of the posterior calcarine arteries.

The cortical area for the reception of the visual impulses lies on the mesial surface of the occipital lobe, extending from the posterior pole to the anterior end of the calcarine fissure. The cortex in this region is characterized by a white line, the line of Gennari, and is known as the

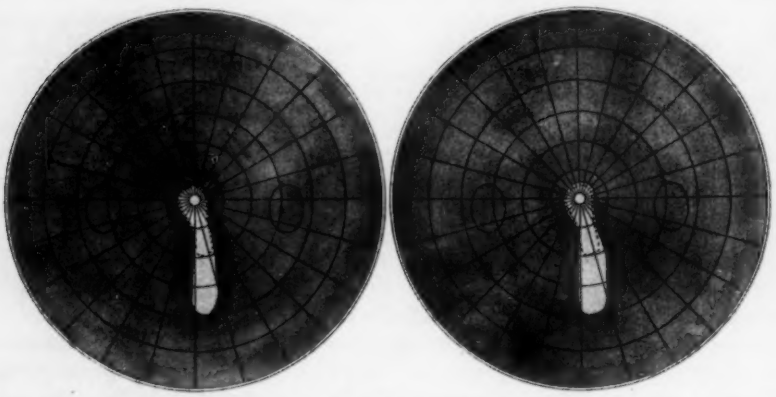

Fig. 1.—Central fields ($\frac{1}{1.000}$ white test object) of patient J. M. The perimetric fields with a $\frac{1}{330}$ white test object were essentially the same.

striate area. Above and below lie the peristriate and the parastriate area; they also extend to the lateral aspect of the occipital lobe. These areas have been associated with visuomotor function (Cords [4]), such as the maintenance of fixation.

The angular gyrus on the lateral aspect of the brain in the posterior parietal region also subserves an important visual function. According to Holmes [5] and Riddoch [6] this area controls many of the higher visual

4. Cords, R.: Optisch-motorisches Feld und optisch-motorische Bahn. Ein Beitrag zur Physiologie und Pathologie der Rindeninnervation der Augenmuskeln, Arch. f. Ophth. **117**:58, 1926.

5. Holmes, G., and Horrax, G.: Disturbances of Spatial Orientation and Visual Attention with Loss of Stereoscopic Vision, Arch. Neurol. & Psychiat. **1**:385 (April) 1919.

6. Riddoch, G.: Dissociation of Visual Perception Due to Occipital Injuries with Especial Reference to Appreciation of Movement, Brain **40**:15, 1917.

functions, such as spatial orientation, visual word memory and stereopsis. It is probably also concerned with the coordination of the reflex ocular movements of fixation (Duke-Elder,[7] Riddoch,[6] Holmes[8]). It has been pointed out by others, however, that for sensory functions one cannot delimit definite centers; there are certain cortical areas which are a part of a complex integrated system. Disturbances of spatial orientation, etc., are probably brought about by interruption of the association pathways between the cortical areas of visual perception and other parts of the brain.

The geographic distribution of the visual field in the visual cortex is now fairly well established (Holmes[9]). There is still considerable argument as to the bilateral representation of the macula, but that need not enter this discussion. The upper and the lower half of the retina are represented respectively in the dorsal and the ventral part of the striate area. The most peripheral part of the visual field, i. e. the unpaired portion of the temporal field, is represented in the most anterior part of the striate area. The macula is represented at the posterior extremity of the occipital lobe, and the area of representation probably extends just beyond the margins to the lateral surface. The intervening homolateral field is represented in serial order between these two regions.

The arterial supply for practically the whole striate area is derived from the calcarine branch of the posterior cerebral artery. Shellshear[10] found that after injection of the posterior cerebral artery and sectioning of the brain, the coloring material in the posterior pole had the same boundaries as the line of Gennari, which defines the striate area. The posterior pole, however, frequently receives an anastomotic supply from the middle cerebral artery. Förster[11] was the first to suggest that this might be the reason for the frequent sparing of the macula in hemianopsia of vascular origin. Figure 2, modified from Whitnall[12] and Shellshear, shows the relationship of the posterior calcarine vessel to the striate area. It can be seen from these diagrams that the middle cerebral artery supplies the superior part of the lateral surface of the striate area. The visual fields[1] are consistent with this fact, as the sparing is in the inferior vertical field.

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7. Duke-Elder, W. S.: Text-Book of Ophthalmology, St. Louis, C. V. Mosby Company, 1932, vol. 1.

8. Holmes, G.: The Cerebral Integration of the Ocular Movements, Brit. M. J. **2**:4045, 1938.

9. Holmes, G.: A Contribution to the Cortical Representation of Vision, Brain **54**:470, 1931.

10. Shellshear, J. L.: A Contribution to Our Knowledge of the Arterial Supply of the Cerebral Cortex in Man, Brain **50**:236, 1927.

11. Förster: Ueber Rindenblindheit, Arch. f. Ophth. (pt. 1) **36**:94, 1890.

12. Whitnall, S. E.: The Anatomy of the Human Orbit, New York, Oxford University Press, 1932.

The patient under consideration presented as his only objective sign a bilateral hemianopsia. Macular vision was spared, and he had 1, 2 and 3 degree stereopsis as measured on the synoptophore; ocular nystagmus in the horizontal and vertical meridians was readily elicited; there was no spatial disorientation or alexia. This patient shows that these higher visual functions are not dependent on the same cortical areas that supply peripheral vision. No doubt there is considerable individual variation in the cerebral vascular circulation. The extent of the cortical damage in all cerebral vascular accidents varies as to the site and the extent of the lesion and of the anastomotic blood supply.

The usual conception of optokinetic nystagmus is that it is elicited by series of moving objects traversing the field of vision. As an object approaches from the periphery and elicits a conscious visual response, the eyes reflexly turn so that it is fixated by the macula. Successive

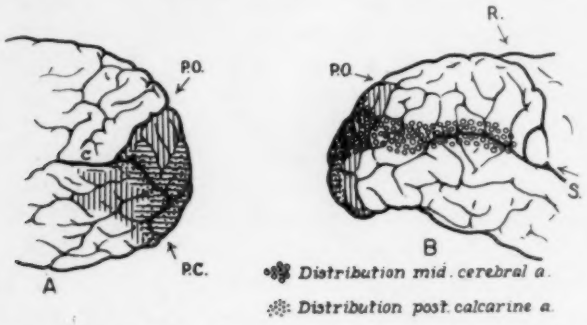

Fig. 2 (from Whitnall and Shellshear).—*A*, medial surface of right occipital lobe. *B*, lateral surface of right occipital lobe. The horizontal hatching denotes the striate area; the vertical hatching, the parastriate and peristriate areas; *C*, the calcarine sulcus; *P.C.*, the terminal part of the posterior calcarine sulcus; *P.O.*, the parieto-occipital sulcus; *R*, the central sulcus of Rolando; *S*, the lateral cerebral fissure (of Sylvius).

objects elicit the jerky movements of the eyes known as nystagmus. One interesting feature in my case was the ease with which optic nystagmus was elicited despite the loss of peripheral vision. This is also borne out in the patient's ability to read without difficulty after the development of his right homonymous hemianopsia. May not the difficulty in reading that usually accompanies right homonymous hemianopsia be caused by some interference with the "fixation reflex" instead of by the reduction of the visual field?

It is fully appreciated that the exact anatomic diagnosis in this case could be made only post mortem. On the basis of previous reports of

cases in which postmortem studies were carried out,[13] I believe that the diagnosis of bilateral occlusion of the posterior calcarine vessels is justified. The patient presented evidence that the "fixation reflex" is not dependent on peripheral vision. Although the area striata apart from that portion subserving macular vision was apparently functionless, optokinetic nystagmus was elicited with ease. This fact may be accepted as evidence that the "fixation center" is probably situated on the lateral surface of the occipital lobe. The integration of the more complex visual functions, such as stereopsis and spatial orientation, is likewise not affected by total loss of peripheral vision. Apparently the performance of these functions is dependent on "macular vision" and certain association pathways not closely connected with the cortical areas supplying peripheral vision.

255 South Seventeenth Street.

13. Bramwell, B.; Bolton, J. S., and Robinson, W.: Bilateral Lesion of the Occipital Lobes with Retention of Macular as Distinct from Panoramic Vision, Brain **38**:447, 1915.

SCLERAL DISEASE IN RHEUMATOID ARTHRITIS

REPORT OF THREE CASES, IN ONE OF WHICH BOTH EYES WERE STUDIED POST MORTEM

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Inflammation of the sclera and of the episclera, the latter first called subconjunctivitis by von Graefe, have long been known to be associated with diseases of the articular structures of the body. Hutchinson [1] in 1885, Fuchs [2] in 1895 and Wagenmann [3] in 1897 reported cases of gout in which episcleritis was a notable complication. Wood [4] in 1936 found crystalline deposits in the sclera of a gouty patient who manifested active scleritis. As recently as 1924, Rateau [5] reported an interesting case in which sclerotenonitis was the prodromal symptom of an attack of rheumatic fever.

In 1938 Verhoeff and King [6] presented a case of rheumatoid arthritis in which an eye was removed because of an inflammatory perforating scleral lesion. This eye was histologically examined in great detail. These authors analyzed 14 previously recorded cases of a similar nature in which the lesion was designated by the name scleromalacia perforans, as suggested in a paper by Van der Hoeve.[7]

While Verhoeff and King stated the belief that their case was the first in which an eye with this disease was examined histologically, I was able to find in the literature a case report by Holthouse [8] in 1893 on a woman aged 71 with rheumatic enlargement of the phalangeal joints and a perforating scleral lesion of the right eye which necessitated its removal. The eye was sectioned, and reference to its pathologic changes will be made later on in this paper.

From the service of Dr. Robert K. Lambert and the Garfunkel Memorial Eye Laboratory, Montefiore Hospital.

1. Hutchinson, J.: Tr. Ophth. Soc. U. Kingdom **5**:1, 1885.
2. Fuchs, E.: Arch. f. Ophth. (pt. 4) **41**:229, 1895.
3. Wagenmann, A.: Arch. f. Ophth. (pt. 1) **43**:83, 1897.
4. Wood, C.: Brit. J. Ophth. **20**:510, 1936.
5. Rateau, J.: Arch. d'opht. **41**:226, 1924.
6. Verhoeff, F. H., and King, M. J.: Scleromalacia Perforans: Report of Case in Which Eye Was Examined Microscopically, Arch. Ophth. **20**:907 (Dec.) 1938.
7. Van der Hoeve, J.: Scleromalacia Perforans, Arch. Ophth. **11**:111 (Jan.) 1934.
8. Holthouse, E. H.: Roy. London Ophth. Hosp. Rep. **13**:415, 1893.

Verhoeff and King composed this clinical description of the disease from a study of 15 cases:

In one or both eyes there develop simultaneously or at intervals slightly elevated nodules involving the sclera and overlying tissue and situated anywhere between the corneal limbus and the equator. Congestion is moderate and is limited to the nodules and their immediate vicinities. After a considerable period, in some cases six months or longer, one or more of the nodules may disappear. At the former site of a nodule there is seen in the sclera a shallow cavity, often of large size. Over a cavity the conjunctiva may be intact or absent. When, as rarely happens, a lesion is situated at the corneal limbus, it may perforate into the anterior chamber and produce a cystoid nodule such as occurs after trephining. Into this nodule the iris may or may not be herniated. When situated elsewhere, the lesions seldom if ever perforate the sclera, and the remaining tissue usually withstands the intraocular pressure, rupturing only in rare instances. Evidences of intraocular inflammation are relatively slight or entirely lacking, unless, as rarely happens, purulent infection occurs at the site of a cavity. Pain may be absent. Posterior synechiae, atrophy of the iris or cataract may occur as late complications in cases of marked involvement. Usually the ocular disease does not occur before the patient reaches the age of 50. In the great majority of cases definite evidences of rheumatoid arthritis exist at the outset of the scleritis.

The purpose of the present paper is to record the history and findings in 3 cases of rheumatoid arthritis in which scleral disease was an outstanding complication and to report the pathologic changes in the two eyes secured for postmortem examination in 1 of these cases.

REPORT OF CASES

Case 1.—A. K., a 50 year old white woman, had been a patient in Montefiore Hospital for the past nineteen years, with an extreme degree of rheumatoid arthritis which had made her completely bedridden and unable even to feed herself, owing to complete ankylosis of all her joints. Roentgen ray examination confirmed the findings.

The ophthalmic history is a long one. In 1927 vision was 20/40 in the right eye and 20/30 in the left, corrected to 20/20 in each with a —1.00 D. sphere. External and fundus examination disclosed nothing abnormal. In June 1932 there developed superficial punctate keratitis of the right eye, which healed with the use of atropine sulfate, ultraviolet therapy and local immobilization. There were no local ocular complaints until May 1936, when nodular episcleritis appeared in the right eye, located superotemporally. Severe bulbar congestion, a violaceous hue of the nodule and marked local tenderness were present. These symptoms persisted until November 1936. There were no further ocular manifestations until July 1937, when the right eye was again affected with episcleritis and a corneal ulcer. The ulcer healed by August, but the episcleritic lesion never left the right eye, and the left eye began to be involved in a similar process. From 1937 until the patient's death in 1941, she was seen by me and by other members of the ophthalmologic staff at intervals of every week or two. The inflammatory signs in the eyes were not appreciably altered by the local or the general treatment instituted, which consisted of atropinization, hot and cold fomentations, diathermy, ultraviolet therapy, administration of large doses of salicylates, application of mercuric ointment and use of epinephrine, ephedrine, butyn, etc.

In the four years from 1937 to 1941, there were frequent remissions and exacerbations of scleritis and episcleritis in both eyes. Often the attacks were associated with superficial ulcers of the cornea. At no time was there any elevation of the intraocular tension, but pain in both eyes was always a prominent complaint. Iridocyclitis with posterior synechias, pigment on the lens capsule and opacities in the vitreous were noted in the right eye in 1938. The pain suffered was apparently due to these causes. Scopolamine hydrobromide had to be used from time to time in place of atropine sulfate, which recurrently caused dermatitis. In October 1939 keratectasia appeared on the temporal side of the cornea of the right eye. Pain, lacrimation and photophobia were constantly present during the acute exacerbations, which lasted over periods of weeks and months.

An examination of the patient's eyes a few months prior to her death in 1941 showed the right eye to be wholly quiescent; pericorneally there were a complete circle of bluish scars, slightly depressed, and one ectatic scar on the temporal side. This eye gave the patient no trouble. The left eye was having a highly acute exacerbation, the scleritic lesion involving the two outer scleral quadrants and extending from the limbus toward the posterior part of the globe, giving the appearance of the brawny type of sclerotenonitis.

The following laboratory data are notable for their negative indications and are given for the sake of completeness. The Wassermann reaction of the blood was negative. A sample of chest fluid taken at the time of a pleural effusion revealed no tubercle bacilli, and pig inoculation gave negative results. The tuberculin test also gave negative results. The sputum showed no tubercle bacilli. The urine was normal. Auricular fibrillation was demonstrated by electrocardiogram.

The patient died in January 1941 during the course of an acute infection of the upper respiratory tract. A complete postmortem examination was performed, and both eyes were secured for histologic study.

CASE 2.—D. K., a 51 year old Austrian-born white man, was first admitted to Montefiore Hospital on Feb. 16, 1934 because of pain in the joints and deformities. There was no history of disease or injury of either eye. The arthritic disease made progressive advances, so that he was confined to bed and chair from 1939 on. Physical examination on June 27, 1940 revealed that he was fairly well nourished, with marked deformity of the joints of the upper extremities and severe stiffness of the spine and neck. Ophthalmologic examination at this time showed no abnormalities. The intraocular tension was normal, and the conjunctivas and corneas were without disease. The pupils were equal and round and reacted sluggishly to light and accommodation. The fundi were entirely normal.

The patient was first seen by me on September 14 because of a purulent discharge from the left eye. Examination now showed the vision to be 20/70 corrected to 20/20 (with a $+1.50$ D. sphere) in the right eye and $20/50-2$, corrected to 20/20 in the left. The intraocular tension was normal; the pupils were equal and reacted well to light and accommodation. The irises were light blue and showed no defects, and the anterior chamber was of normal depth in each eye. There was no discharge on expression of the lacrimal sacs; the conjunctival vessels of the lids were moderately injected. The fundi showed simple arteriosclerosis.

The chief pathologic change was found in the sclera. In the right eye, from 11 to 2 o'clock and extending toward the equator for 12 mm. was a slightly raised, fairly well demarcated patch, purplish in color and completely insensible to touch; the episcleral vessels posterior to the episcleritic process were dilated. The con-

junctival vessels over the site of the episcleritis were engorged. Slit lamp examination of the right eye showed no evidence of uveitis and nothing more than severely dilated episcleral and conjunctival vessels.

In the left eye the episcleritic process was more expansive, extending from 9 o'clock at the limbus to 4 o'clock and backward far beyond 12 mm., merging with a generalized hyperemia of the tissue and giving the appearance of a brawny tenonitis. Slit lamp examination of the left eye also showed no uveal involvement and disclosed the same conditions of vascular dilatation. The episcleritic tissues involved were slightly raised and also remarkably insensitive to touch and caused

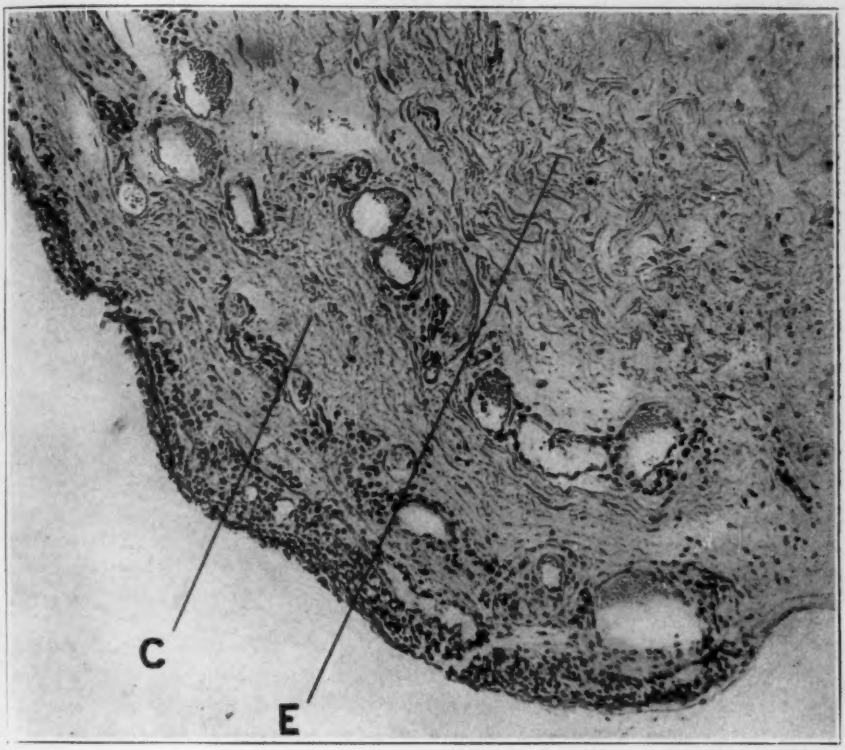

Fig. 1 (case 2).—Biopsy specimen of episcleral tissue: *C*, conjunctiva, showing subepithelial perivascular round cell infiltration; *E*, episcleral fibers separated by edema.

no spontaneous pain. The intern made a note on the chart referring to the "remarkable absence of pain."

A biopsy was done on the left eye at the temporal side, where a 5 mm. piece of episclera and conjunctiva was excised. With a hematoxylin and eosin stain, the conjunctiva showed a perivascular mononuclear lymphocytic infiltration in the subepithelial layers and below this a severe edema which separated the episclera into laminas interspersed with mononuclear cells (fig. 1).

Pus from the left eye was taken for smear and culture. The smear showed a few gram-positive cocci in pairs and a few gram-positive bacilli. The culture consisted of diphtheroids and Staphylococcus albus.

The Wassermann and Kahn reactions were negative. The blood contained per hundred cubic centimeters: urea nitrogen, 13.4 mg., uric acid 3.8 mg., cholesterol 167 mg., calcium 11.1 mg., phosphorus 4.4 mg., total protein 6.9 mg., albumin 1.9 mg. and globulin 5.0 mg. The hemoglobin content was 79 per cent. The red blood cells numbered 4,630,000 and the white cells 16,900. The sedimentation rate was 29.

CASE 3.—S. B., a 44 year old white woman, had been a patient in Montefiore Hospital for the past seven years. Her illness began in July 1929 with polyarthritis. This was followed by symptoms of cardiac disease, later diagnosed as constrictive pericarditis, and bilateral hydrothorax which required tapping. In 1935 there developed periarticular nodules which on biopsy were called cellular neurofibromas. Deformity of a fusiform character occurred in the proximal interphalangeal joints, with pain and stiffness in all other joints, so that a diagnosis of rheumatoid arthritis appeared to be established. About the ankles, elbows and wrists there were small, firm, movable subcutaneous nodules, which according to the patient came and went.

Ophthalmologic examination in 1934 revealed the vision to be 20/70 in the right eye and 20/50 in the left, corrected to 20/20 in each eye with a —1.50 D. cylinder, axis 180. External and internal examination of each eye did not show the existence of any pathologic process.

The patient's present ocular complaint began in August 1940 with itching, burning and lacrimation of both eyes and sticking together of the eyelids when she awakened in the morning. Ocular examination at this time disclosed prominence of the globes and ocular motility without limitation. The intraocular tension was normal. External examination of the right eye revealed a typical violaceous episcleritic patch of inflammation situated slightly away from the limbus, extending from 10 to 12 o'clock and posteriorly about 10 mm., but not too well defined. The patient did not complain of pain, and the superficial episcleritic patch was not tender to touch. Slit lamp examination revealed nothing more than dilatation of the ciliary and conjunctival vessels. For eight months the episcleritis remained the same in color and in extent; then it lightened in color, owing apparently to a decrease in the number of dilated vessels. The whole process was mild and involved only the episclera.

The pathologist's report of the biopsy of a subcutaneous nodule was as follows: "The nodule is small and covered by stratified squamous epithelium. In the corium there are numerous lymphocytes, and in the depth of the tissue there is a fairly well circumscribed nodule composed of densely packed cells. These cells have an indistinct cytoplasm which forms an irregular syncytium. Lipoid material is apparently present within the cytoplasm. Nuclei are spindle shaped and round and show moderate pleomorphism. Thin strands of collagenous material are present in some portions of the tumor. There is a large quantity of double-refractile material within the tumor."

The reaction to old tuberculin test 1:10,000 was positive in 1941 but not in 1939. Guinea pig inoculation with gastric contents disclosed no evidence of tuberculosis. The blood contained per hundred cubic centimeters: urea nitrogen 12.7 mg., cholesterol 312 mg., total protein 717 mg., albumin 3.7 mg., globulin 4.0 mg. and calcium 10.0 mg. Studies of the bone marrow revealed nothing abnormal; no xanthoma cells were seen. The Wassermann reaction was negative. The vitamin C content of the urine was 41 mg., indicating an adequate intake of vitamin C.

HISTOLOGIC EXAMINATION OF THE EYES IN CASE 1

Laboratory Procedure.—Both eyes were fixed in Müller's solution and run through alcohol—50, 70 and 80 per cent—for three days. The left eye was halved, being cut from cornea to optic nerve, and the right eye was cut along the equator. The specimens were then fixed in 96 per cent alcohol for one week, absolute alcohol for one week, chloroform-alcohol for eight hours, chloroform overnight, chloroform-paraffin for eight hours, petrolatum overnight and paraffin for three hours. Sections were cut 7 millimicrons thick and stained with hematoxylin and eosin and trichrome stain. Bacterial stain revealed no organisms.

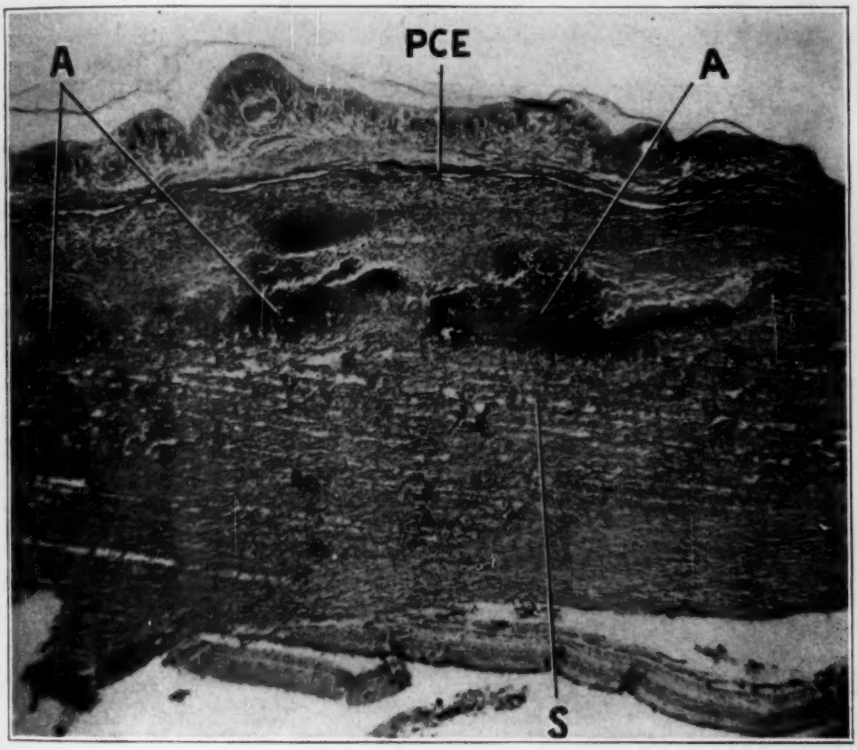

Fig. 2 (case 1).—Section of the right eye: *S*, sclera; *A*, large abscesses; *PCE*, pigmented ciliary epithelium.

Microscopic Examination.—Right Eye (section midway between the cornea and the equator): At the site of the scleral lesion (fig. 2) the sclera was 3 to 4 mm. thick for a distance of approximately 14 mm. Within the substance of the sclera in this region there could be seen four large and numerous small areas of cellular necrosis which appeared like walled-off abscesses (fig. 3). Each abscess consisted of a central mass of disintegrating scleral fibers together with pus cells, which in many places were completely fragmented and reduced to a shapeless mass. The abscesses were bounded by epithelioid cells, plasma cells and intact scleral fibers; occasional giant cells and numerous lipoid-carrying foam cells could be found in some of the abscesses. Outside the abscesses proper, particularly in

the episcleral tissue, there are found in the spaces between the scleral fibers numerous plasma cells, lymphocytes and fibroblasts. Practically nowhere in the vicinity of the abscesses was there any evidence of new blood vessel formation or free pus cells, and not one of the numerous abscesses showed evidence of organization.

The conjunctiva overlying the area of the scleral abscesses showed slight edema and slight round cell infiltration. The uvea underlying the scleral lesion was involved in the inflammatory process and was fused indistinguishably with the scleral inflammatory tissue, being replaced by fibrous tissue and inflammatory cells, chiefly plasma cells and large mononuclear cells. The pigmented layer of the ciliary epithelium was broken through in numerous places, and pigment was scattered between the uvea and the sclera.

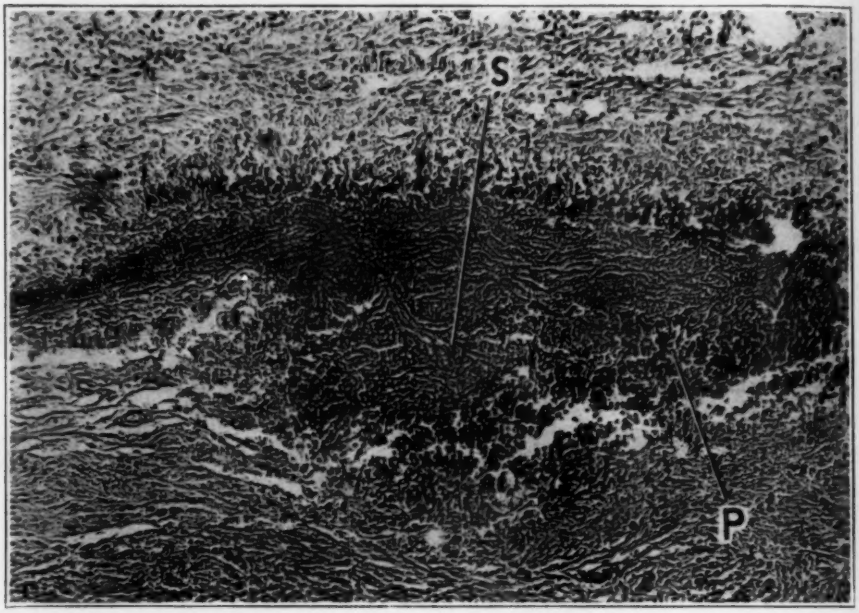

Fig. 3 (case 1).—High power view of *AA* of figure 2, showing an area of sclera (*S*) surrounded by pus cells (*P*).

Left Eye (section through the cornea and the optic nerve): The corneal stroma was markedly distorted (artefact), and the fibers were separated by wide empty spaces; the corneal epithelium was in part torn off. The iris angle and the anterior chamber were normal. Deep in the substance of the sclera (fig. 4) were two large abscesses, the anterior one impinging on the ciliary body and being the larger of the two. The posterior abscess lay beyond the ora serrata. Each abscess in its center was composed of necrotic scleral shreds and polymorphonuclear cells in various stages of destruction. There were large phagocytes present, as well as numerous round cells, chiefly plasma cells and epithelioid cells on the periphery of the abscess. The anterior and larger abscess already showed a cavity in which a separating sequestrum in complete granular disintegration could be seen (fig. 5).

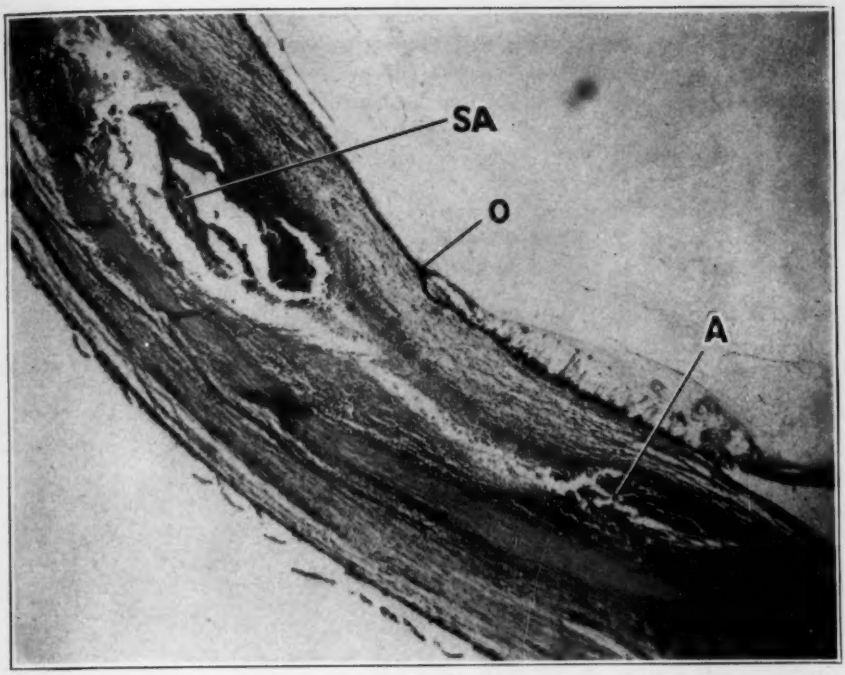

Fig. 4 (case 1).—Section of the left eye: *AA*, large scleral abscesses, with a sequestrum (*S*) in one; *O*, ora serrata.

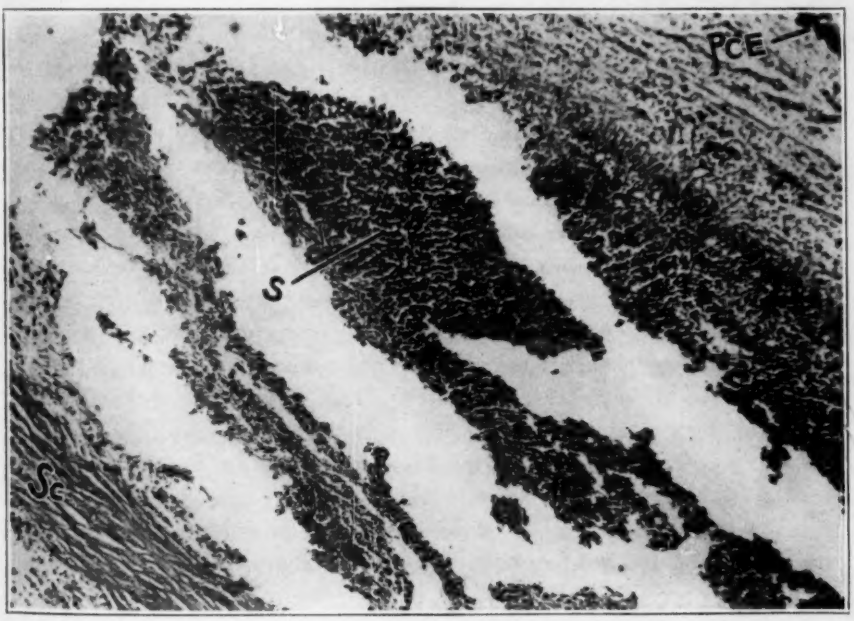

Fig. 5 (case 1).—High power view of *SA* of figure 4, showing the center of the broken-down abscess: *Sc*, scleral fibers; *PCE*, pigmented ciliary epithelium; *S*, sequestrum.

Superficial to the abscesses, the sclera and the episclera were infiltrated with plasma cells and lymphocytes. Posterior to the smaller abscess, the sclera was infiltrated with round cells and plasma cells and was thickened to a point about the equator where the sclera resumed its normal appearance. The deep scleral tissue adjacent to the abscesses showed the same mononuclear cell infiltration with an occasional pus cell. The ciliary body and processes were remarkably free from signs of inflammation in spite of the proximity of the large anterior abscess. No significant histologic changes were noted in the remaining ocular structures.

COMMENT

The pathologic changes of the scleral disease associated with rheumatoid arthritis appear to consist of multiple, disseminate and discrete areas of focal necrosis together with an inflammatory reaction of a subacute type leading to formation of relatively large abscesses. These abscesses show no tendency to become vascularized or organized but, contrariwise, tend to become reduced to cavities containing formless debris or a sequestrum. Verhoeff and King mentioned 2 cases in which a sequestrum was seen clinically within a scleral cavity, and one was removed and proved to be hyalinized scleral tissue. The same authors postulated the pathogenesis of such scleral abscesses to be as follows:

An area in the sclera first undergoes simple necrosis. This area soon becomes surrounded by a wall of epithelioid cells. Pus cells then slowly penetrate the wall and surround and infiltrate the necrotic area, which has become more or less disintegrated into eosinophilic granules. Ultimately, the sequestrum thus formed becomes completely disintegrated and densely infiltrated with pus cells, which also become necrotic.

The pathologic changes in the eyes in case 1 can readily be ascribed to such an evolution.

It is remarkable that none of the abscesses in either eye in case 1 ruptured the sclera either from within or from without in spite of the long duration of the clinical symptoms of scleritis (five years).

Holthouse in 1893 treated a woman of 71 with "rheumatic" joints who had an inflammatory swelling on the inner scleral side of the right eye which had been present for five months and which was ulcerated in two places. Her pain was severe, and enucleation was advised but rejected. Three years later the eye was much shrunken, pain was constant and the eye was enucleated. The shrunken globe showed a break in the continuity of the sclera and the cornea, through which a nodular mass protruded. In the episcleral tissue on each side of the cornea, the blood vessels were dilated and there was present a thick round cell infiltration. A mass of round cells filled the gap in the sclera, and the gap had extended through the ciliary body. The posterior part of the choroid was healthy, but the anterior part showed a moderate

infiltration with round cells. No giant cells or tumor cells were reported. The scleral lesion in this case had ruptured internally as well as externally. Although the pathologic changes were not reported in great detail, probably owing to the distortion of the globe, yet the clinical site of the lesion, its ulceration and its occurrence in a case of rheumatoid arthritis make it highly probable that this is the first case on record of a perforating scleral abscess in rheumatoid arthritis. The disease process certainly conforms to the essential pathologic change observed in the case reported by Verhoeff and King and in my case 1.

The question might be asked if there is anything specific in the histopathologic process of eyes suffering with scleritis in the course of rheumatoid arthritis. A categorical answer cannot be given from the evidence found in the cases of Holthouse and of Verhoeff and King and in my case. Although the pathologic process in my case and in that of Verhoeff and King were identical, a conclusion that this is specific is not justified, for the reaction of the tissue involved (sclera) would appear to play a great part in the histologic end results. The sclera is a fibrous and almost avascular structure, and pathologic processes affecting it are chronic and torpid in character and very resistant to therapy. When the sclera proper becomes involved, the tissues adjacent to it take over the role of a vascular system, but often they are too far away from the damaged scleral fibers, which then rapidly become necrotic, with no chance for organization or repair. If the lesion is near to the episclera or the uvea the chances for replacement by fibroblastic tissue are correspondingly greater. It is thus possible for various changes to take place in the sclera in response to activating agents, ranging from deeply lying unorganized abscesses with sequestrums to more superficial scleral lesions showing phagocytic and fibroblastic activity. My patient showed this repair activity away from the depth of the lesions. The type of scleral lesion will therefore depend on the proximity of an adequate circulation to the affected tissues.

Verhoeff and King examined sections of eight subcutaneous nodules removed from patients with rheumatoid arthritis and found the pathologic changes to be strikingly similar to the initial scleral lesions. The biopsy of the subcutaneous nodule in my third case showed a nodule of densely packed mononuclear cells with lipoid material in the cytoplasm but no areas of necrosis.

The term scleromalacia perforans is not accurately descriptive of the disease, and a better name was suggested by Verhoeff and King. Necroscleritis nodosa excavans, with the last term excluded when no perforation occurs, ought to be adopted, since it more completely describes the clinical and the pathologic nature of the disease.

SUMMARY

Three cases of rheumatoid arthritis complicated by scleral involvement are presented.

The pathologic changes in both eyes in case 1 consisted in large abscesses deep in the substance of the sclera and multiple minute areas of necrosis and cellular reaction in the sclera but not much beyond the ora serrata.

The clinical and the pathologic observations in case 1 of this paper are in all respects identical with Verhoeff and King's clinical description of the disease and the pathologic changes they observed in an eye removed in a case of this disease.

Bacterial staining of the eye sections in my case 1 and in the case of Verhoeff and King revealed no micro-organisms.

CONCLUSION

Whatever the primary cause of rheumatoid arthritis may be, it is probable that the scleral lesions and the subcutaneous nodules are similar in nature, and the characteristic pathologic process observed in the eye may be due to the peculiar nature of the avascular tissue (sclera) involved.

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EMMETROPIA

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Before the middle of the nineteenth century, there was a vague understanding of some of the refractive states of the eye. Myopia, with its obvious symptom of poor distant vision, had been recognized since ancient times and was accurately defined by Kepler in 1611. Presbyopia, with the inability to see near objects in old age, had long been noted but was confused with hypermetropia. What is now known to be hypermetropia was suggested by Kästner in 1755 but was not well understood until about a century later. The accepted conception of accommodation was presented by Thomas Young in 1801, and, to complete the dioptric faults, the presence of astigmatism was demonstrated by George Airy in 1827.

The conditions present to constitute a normal refractive state received but scant attention by the older writers, owing to a lack of knowledge of the exact ocular structure and manner of functioning. Progress was made in the understanding of the operation of the retina when Treviranus, in 1835, proposed that the rods and cones were the ultimate structures of vision, and this theory was further advanced when H. Mueller and Kölliker, in 1852, found that they were connected with the optic nerve. That some thought had been given to a normal refractive state is shown by a quotation from the work of Mackenzie[1]:

> It is only, however, by that degree of refraction, or with that form of the eye, which permits the rays of light, proceeding from the luminous points of objects, to be brought into corresponding or nearly corresponding focal points upon the retina, that perfect vision can be produced.

About one hundred years ago the refractive errors of the eye were placed on a sound clinical basis by the work of Donders and Helmholtz, whose writings have since been the guide of those who practice ophthalmology. That a normal refractive state of the eye should be considered was recognized by Donders,[2] and he named it emmetropia, "from ἔμμετρος, modum tenens, and ὤψ, oculus." For this state he gave as the definition:

> The emmetropic eye is that, the principal focus of whose dioptric system is, in rest of accommodation, found in the retina. Of infinitely remote objects, which send

1. Mackenzie, W.: Diseases of the Eye, ed. 3, London, Longman, Orme, Brown, Green & Longmans, 1840, p. 778.

2. Donders, F. C.: On the Anomalies of Accommodation and Refraction of the Eye, translated by W. D. Moore, London, New Sydenham Society, 1864, pp. 81 and 173.

out parallel rays, this retina therefore receives *accurate images,* to be improved neither by convex nor by concave glasses, and by means of its accommodation it sees equally accurately at relatively short distances.

This name and description have been accepted by all authorities since it was presented, only being given a different wording, as is seen by quotations from some of the latest textbooks:

We have seen that in the physiologically normal eye parallel rays converge upon the retina to form a circle of least diffusion; when these ideal optical conditions occur with the eye in a state of rest the condition is termed *emmetropia.* (Duke-Elder.[3])

When the retina lies in the plane of the posterior principal focus of the dioptric system of the static eye the condition is called *emmetropia.* (Cowan.[4])

Emmetropia literally means "an eye in measure," or an eye which has reached that stage of development where parallel rays of light will be focused on its retina without any effort of accommodation. (Thorington.[5])

When parallel rays are focused exactly on the retina with the eye in a condition of rest, the refraction of the eye is normal or *emmetropic* and the condition is known as emmetropia. (May.[6])

An eye which is so formed that parallel rays of light are focused on the retina without an effort of accommodation is known as an *emmetropic* eye, while all others are *ametropic.* (Gifford.[7])

This conception of emmetropia is undoubtedly correct, although possibly incomplete, as parallel rays are focused on the retinal layer of rods and cones in the absence of accommodation; but it seems to me that an important physiologic process also plays a part in placing the focus on the retina to constitute emmetropia, and this is the normal tonus of the ciliary muscle.

Physiologists teach that there is a sustained state of partial contraction of all the muscles of the body, known as tonus, or postural contraction. This is abolished by section of the motor nerve. Sustained contractions may be increased by abnormal conditions, the state being designated as spasticity. Smooth, or involuntary, muscle is widely distributed in the organs of the body and is controlled by the autonomic nervous system. It acts as a sphincter at many places and functions properly throughout life unless weakened by disease or thrown into spasticity by irritation. In the eye there is a similar collection of smooth

3. Duke-Elder, W. S.: The Practice of Refraction, ed. 2, Philadelphia, P. Blakiston's Son & Co., 1935, p. 68.

4. Cowan, A.: Refraction of the Eye, Philadelphia, Lea & Febiger, 1938, p. 136.

5. Thorington, J.: Methods of Refraction, ed. 3, Philadelphia, P. Blakiston's Son & Co., 1939, p. 146.

6. May, C. H.: Diseases of the Eye, ed. 16, Baltimore, William Wood & Company, 1939, p. 362.

7. Gifford, S. R.: A Textbook of Ophthalmology, ed. 2, Philadelphia, W. B. Saunders Company, 1941, p. 48.

muscle in the ciliary body and iris, which is governed by the same physiologic processes as smooth muscle elsewhere.

The autonomic nervous system has received considerable attention of late, and much material of value has been discovered as to its manner of functioning; but it is believed that more remains to be found. Much that is known is of interest to ophthalmologists, as many of the experiments are on the eye and most of the drugs used are constantly employed in this specialty. Those that stimulate accommodation, like acetylcholine and prostigmine, are cholinergic; while those that cause its paralysis, such as atropine and benzedrine, are adrenergic.

The existence of tonus of the ciliary muscle is proved by the changed refraction in paralytic conditions due to disease and by the effects of cycloplegics. Tonus is a well known fact, and its presence and action have been noted by writers since the time of Donders, but it is a question whether the role it plays has received its due consideration. The amount of tonus exerted by the ciliary muscle can be measured by its relaxation by a cycloplegic: by testing the refraction when the subject is under its influence and again when its effect has worn off. Experience shows that this amount is equal to about 1 D. as measured by lenses, producing 1 D. more than a manifest hypermetropia and 1 D. less in myopia. Possibly the amount may vary in high refractive states, being greater in hypermetropia and less in myopia.

There is a condition that I think should be distinguished from tonus, and that is latent hypermetropia. With a subject under a cycloplegic an additional 1 D. is found, which is added to the amount of manifest hypermetropia to make what is considered the total hypermetropia. When tonus is restored and the eye is in a physiologic state, this latent hypermetropia does not exist.

There is probably a distinction to be made between tonus and accommodation. Tonus when normal is an ever present contraction of the ciliary muscle of a constant amount and involuntary in its action. Accommodation is absent until called into play by a voluntary impulse and is of an amount necessary to focus the eye at different distances. Accommodation fails with age but probably more from lenticular changes than from a weakening of the ciliary muscle. Tonus should also endure, as it does in other sphincters, but its activity may be abolished by advanced sclerosis of the lens.

The problems of refraction would be easier to solve if tonus were always normal, but there are two abnormal conditions which must be investigated. One of these is an overactive state of the ciliary muscle, or spasticity; the other is a weakening of the muscle, or atonicity. The term cyclospasticity might be used to designate the state in which the ciliary body is affected and miosis be confined to change in the iris, just

as the difference is recognized between cycloplegia and mydriasis. Spasticity is caused by irritation from disease; by drugs, such as physostigmine, and by overuse of the eyes at close work, especially by persons with high degrees of hypermetropia. This spasticity may conceal the hypermetropia or even simulate myopia. It is well known that this process occurs, but in my experience it does not occur as often as some authorities claim. The spasticity does not relax to lenses alone but is found on use of a strong cycloplegic, such as atropine sulfate; therefore, it may be a spastic state of tonus and not spasm of accommodation.

Atonicity, or asthenia, known as accommodative asthenopia, occurs in toxemias and in debilitated states and is indicated by the inability of the patient to do continuous close work. Paralysis of tonus is caused by diseases and by drugs and is easily detected, as accommodation is also lost. Careful observation may show that in atonicity the cycloplegic tests may indicate less than a normal tonus.

There are no instructions in the textbooks for special tests to determine whether tonus is normal or abnormal, and they are not necessary, as these conditions are found, and can be understood, in the usual refraction routine.

Emmetropia is considered to be the perfect refractive state of the eye. It has no relation to vision, as any degree of amblyopia may be present, even to blindness. Whether the eye attains this perfection, or only rarely approaches it, it must be adopted as a standard for measurement of departures from the normal. The eye is unique in comparison with the other organs of the body in that it must more nearly conform to a standard of size, shape and tissue construction to function accurately.

At birth no other part of the body is as near the mature size as the eye, with the possible exception of the ossicles and the internal ear. The eye also reaches its full development earlier than other organs. Some authorities place the age for its doing so at about 10 years, but distant vision is normal and much close work can be done at an earlier period. Many persons pass over into myopia before the age of 10, but objection might be raised to considering them as a standard. An extensive survey would be necessary to show when the young hypermetrope reaches emmetropia.

There are four factors in the eye which by their combined action constitute emmetropia: the size of the eyeball, which gives the axial length; the curvature of the cornea and the lens, for the refractive power; the refractive index of the cornea, aqueous, lens and vitreous, and the tonus of the ciliary muscle. The combination of these factors being correct, the image is focused on the retina. The first three constitute the dioptric system, the action of which is physical, and the tonus of the ciliary muscle is physiologic; so the complete process is physicophysio-

logic. If tonus is always present in the normal state it must be included; therefore, as a definition it is proposed that: Emmetropia is the refractive state of the eye when rays of light parallel to the principal axis of the dioptric system are focused on the retina when acted on only by the normal tonus of the ciliary muscle.

While all the writers of textbooks give a definition of emmetropia, there is no exact instruction as to a method to establish its presence. Knowing that abnormalities may be present, they advise a cycloplegic test. If in this test only a + 1 D. sphere is needed the diagnosis of hypermetropia, the so-called latent hypermetropia, is made. If no lens is accepted during cycloplegia but a — 1 D. sphere is accepted afterward, the refractive state is recognized as myopia. Thus during cycloplegia there is no state that can be called emmetropia. This fact is confusing to the student, who may conclude that the eye which accepts no correction during cycloplegia, but is really myopic, is emmetropic. He may be more perplexed by reading: "An emmetrope, if atropinised, still maintains perfect distant vision."[8]

If tonus were always normal it would be easy to determine the presence of emmetropia simply by the blurring with a weak plus sphere or the lack of improvement with a minus sphere. But, owing to the possibility of abnormal tonus, a test to give positive results must be made during cycloplegia. The results must then be compared with the findings after the cycloplegic has ceased to act and must be properly interpreted. If during cycloplegia only a + 1 D. sphere is accepted and afterward nothing is required, the eye is emmetropic and tonus is normal.

There are periods during the life of certain persons when emmetropia is only temporary. The hypermetropic eye of infancy should develop to emmetropia and then stop, but for some reason, as yet not positively established, it grows on into myopia. A temporary emmetropia may occur later in life during a refractive change from hypermetropia to myopia in the progress of the development of a cataract. Also, a reversed change may occur in adult life when a slight myopia is being converted to hypermetropia because of lenticular changes. Probably the period of emmetropia is of a comparatively short duration in all these circumstances, but it is in evidence if the examination happens to be made at the time.

Astigmatism is also classed among the ametropias and when present is considered to rule out emmetropia, but if neither a plus nor a minus sphere is needed, then one meridian is emmetropic. The eye is of practically normal size and by a liberal view can be considered emmetropic if the astigmatism is slight.

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8. Juler, H. E.: Ophthalmic Science and Practice, ed. 3, Philadelphia, Lea Brothers & Co., 1904, p. 476.

Nearly all authorities agree that such a refractive state as emmetropia can exist, but they are also of the opinion that it is rare. Some investigators deny its presence, as shown by the following quotations:

An "emmetropic pair of eyes does not probably exist. (Gould.[9]) I have never seen a pair of eyes without some ametropia. (Gould.[10])

We might premise that there is no such thing as an emmetropic eye, approximately, yes, absolutely, no. (Smith.[11])

There are very few absolutely emmetropic eyes, and any practitioner could count on the fingers of one hand the number of cases in which, after paralysis of the ciliary muscle under repeated doses of a strong mydriatic, the distant vision of apparent emmetropes could not be perceptibly improved by the use of a weak cylindrical or spherical convex or concave glass. (Norris and Oliver.[12])

If the emmetropic eye be considered, as it scientifically should be, as a perfect visual mechanism, in which parallel rays of light are brought to a focus exactly on that part of the retina devoted to distinct vision when the eye is in a state of rest, it is doubtful that it has any existence at all. The emmetropic eye, as it is clinically seen at times, is but a temporary condition in what is known as diminishing hypermetropia—the transitional stage beween hypermetropia and myopia, a refractive halt in an irritated or inflamed eye that needs treatment. (Ball.[13])

It would be strange if this were a common state of affairs. It must be remembered that its attainment depends on the exactitude to within a fraction of a millimetre of such measurements as the length of the eye and the shape of the cornea and lens; and such regularity and conformity to type as optical perfection would necessitate, demands a mathematical accuracy which is nowhere realized in the constitution of living organisms. Emmetropia may be optically normal, but it is no more biologically normal than would be the universal attainment of a uniform height of five feet six inches. (Duke-Elder.[3])

Those who deny the existence of emmetropia may consider the presence of the slightest degree of astigmatism — even 0.12 D. — as removing the subject from the normal class. The finding of + 1 D. sphere during cycloplegia also increases the number of persons considered to be ametropes, but their eyes function normally. If one considers as normal those persons who show a normal tonus under a cycloplegic and accept no spherical lens afterward, then the incidence of emmetropia may be considerably increased.

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9. Gould, G. M.: Biographic Clinics, Philadelphia, P. Blakiston's Son & Co., 1909, vol. 6, p. 420.

10. Gould,[9] 1907, vol. 5, p. 15.

11. Smith, H. E.: Applied Refraction, New York, William Wood & Company, 1927, p. 45.

12. Norris, W. F., and Oliver, C. A.: A Text-Book of Ophthalmology, Philadelphia, Lea Brothers & Co., 1893, p. 382.

13. Ball, J. M.: Modern Ophthalmology, ed. 5, Philadelphia, F. A. Davis Company, 1926, vol. 2, p. 1181.

A large group of young persons, such as college students, would provide a good statistical study, but there might be some difficulty in subjecting them to cycloplegic tests. Office and clinic data would naturally show a larger proportion of ametropes.

The meticulous view that is so generally held that nature has failed to approach the normal in the visual organ should be replaced by one that admires her handiwork, which is so near perfection in many instances.

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CLINICAL SIGNIFICANCE OF ANISEIKONIA

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I. INTRODUCTION AND DEFINITIONS

The two eyes are never identical. Between them there are always numerous discrepancies in the neuromuscular apparatus, the dioptric system and the sensorial apparatus. The discrepancies of the neuromuscular apparatus, the heterophorias, cause a faulty relative position of the eyes when fusion is suspended. The aberrations and other irregularities of the dioptric system cause faulty dioptric images, which in some cases may differ considerably in the two eyes. Furthermore, the differences in the relative position of objects in space and in their distance from the two eyes cause geometrically different images to be formed in the two eyes. The discrepancies of the sensorial apparatus are caused by a special distribution of the receptor elements.

As a result of all these discrepancies and incongruities, the two ocular images [1] of the visual system are different even under normal conditions. The incongruities as a rule are overcome by processes of physiologic adaptation or psychologic interpretation, and the two ocular images can be fused readily into a single mental image. Indeed, some incongruities are the necessary basis for normal binocular vision and spatial localization (depth perception). But when these incongruities exceed a certain amount they present a more or less serious obstacle to fusion and may produce pathologic symptoms requiring treatment.

This fact has been generally recognized as true for the incongruities of the neuromuscular apparatus, the heterophorias. It is less well known with regard to the incongruities of the ocular images which are a result of the anomalies either of the dioptric apparatus or of the sensorial apparatus of the eyes or of both.

The members of the Dartmouth Eye Institute have paid special attention to the last-mentioned type of incongruity, and the purpose

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From the Dartmouth Eye Institute, Dartmouth Medical School.

Read before the Section on Ophthalmology of the New York Academy of Medicine on Jan. 20, 1941 and before the Section on Eye, Ear, Nose and Throat of the Academy of Medicine of Northern New Jersey on Jan. 12, 1942.

1. Ocular image is used to describe the impression which reaches consciousness through the vision of one eye. It is determined not only by the properties of the dioptric image that is formed on the retina of the eye but by the modifications imposed on that image by the anatomic and physiologic properties of the structures by which it is carried to the higher brain centers.

of this paper is to discuss the practical value of the theoretic knowledge and the clinical experience gained in the work on aniseikonia.

Aniseikonia is defined as a difference in the size and/or shape of the ocular images. It must be emphasized that it is not a matter of absolute size, but of the relative size of the ocular images, and aniseikonia is, therefore, a condition affecting binocular vision.

Differences in the ocular images may be caused by differences in the dioptric images. In cases of refractive anisometropia,[2] for instance, corrective refractive lenses of different power located at the same distance in front of each eye will give rise to the formation of images of different size on the two retinas. This fact has long been known, but no attempt was made to equalize the dioptric images. It is a new concept that a difference in the size of the ocular images may also exist in cases in which there is no difference in the size of the dioptric images. The ocular images are frequently different in size even if both eyes are emmetropic. This type of difference may be termed basic aniseikonia in contradistinction to a refractive aniseikonia introduced by lenses. The two types may be present in the same person; consequently, in cases of anisometropia one often finds that the amount of aniseikonia measured differs from the amount which would be expected theoretically. It is larger if the basic aniseikonia is in the same direction as the artificially introduced aniseikonia and smaller if the basic aniseikonia is in the opposite direction. Because of the existence of a basic aniseikonia, and because it is not known whether the ametropia is axial or refractive, the amount of aniseikonia in a case of anisometropia cannot be predicted but has to be determined by measurement.[3]

Aniseikonia is a general term covering all the incongruities of the ocular images. An analysis of the different types of incongruities shows that the ocular images may be different in all meridians (over-all size difference) or that one of the two images may be different only in the horizontal or vertical meridian (meridional size difference). There may also be a difference in size in the oblique meridians (oblique meridional size difference). Moreover, the images may be asymmetrically different in the two eyes (for instance, in one eye larger on the temporal and smaller on the nasal side—an asymmetric size difference); they may be irregular in their differences, or, finally, two or more of these incongruities may be combined.

The various groups of anomalous incongruities are listed in table 1, but in this paper I shall consider mainly the over-all size differences

2. In the case of axial ametropia (and anisometropia) the lenses correcting the refraction do not cause a change in the size of the dioptric images if their second principal points coincide with the anterior focal points of the eyes.

3. Carleton, E. H., and Madigan, L. F.: Relationship Between Aniseikonia and Anisometropia, Arch. Ophth. **18**:237 (Aug.) 1937.

and size differences in the principal meridians. The other groups can also be measured and are undoubtedly of considerable theoretic and practical importance,[4] but neither their determination nor their correction has as yet attained the status of clinical routine. Therefore they will not be discussed at this time.

II. DISTURBANCES AND SYMPTOMS CAUSED BY ANISEIKONIA

In accordance with the nature of aniseikonia, its presence causes difficulties in the act of fusion and in binocular spatial localization.

For an object to be seen singly with both eyes, the images formed in the two eyes must be fused into one mental image. The greater the similarity between the images of the two eyes, the easier is this act of fusion. A measurable difference in the size of the two ocular images presents an obstacle to fusion, and in this respect aniseikonia is comparable to the heterophorias.

TABLE 1.—*Anomalous Incongruities of the Ocular Images*

1. Over-all size differences
2. Meridional size differences
A. In the principal meridians
(*a*) In the horizontal meridian
(*b*) In the vertical meridian
B. In oblique meridians
3. Asymmetric size differences
4. Irregular size differences
5. Combination of two or more

Every one has some aniseikonia, just as every one has some heterophoria. Heterophoria may be compensated for by physiologic adjusting mechanisms, and there is evidence that low amounts of aniseikonia can be similarly overcome. It is well known to every ophthalmologist that some otherwise normal persons are able to overcome a surprisingly high amount of heterophoria. Such persons show large fusional amplitudes. But if a person has small fusional amplitudes relative to his heterophoria, or if his general resistance is lowered, asthenopic symptoms may occur. He may then even see double, i. e., give up binocular vision altogether.

Aniseikonia may in a similar way produce asthenopic symptoms; it will depend on the patient's tolerance to size differences whether or not subjective symptoms will arise. If his tolerance is high it is less probable that he will experience asthenopic symptoms than if his tolerance is low.

The symptoms of which the patients complain most frequently are listed in the first part of table 2. These symptoms in themselves are

4. Highly interesting experimental and clinical material on these incongruities will be published in the near future by Prof. Adelbert Ames, Jr., Prof. Kenneth N. Ogle and Dr. Walter B. Lancaster.

not characteristic of aniseikonia: They are common to all patients having asthenopia, regardless of its origin. Certain combinations, however, seem to be more frequent when aniseikonia is the cause of the trouble. Wendell L. Hughes pointed out that photophobia is an unusually frequent complaint [5] in his series of aniseikonic patients and that headaches combined with photophobia are a suggestive combination of symptoms.[6] He also stated that trouble in viewing moving objects and general physical symptoms are more frequent in patients having aniseikonia.[7] Hughes emphasized, furthermore, that the greater the number of symptoms a patient has, the greater the likelihood of aniseikonia.[8]

All asthenopic symptoms are usually more severe when a full correction of high anisometropia is attempted. In most instances it is impossible to prescribe a full refractive correction for both eyes, because this correction causes the patient to have discomfort, eyestrain and even diplopia. This well known fact is usually explained on the basis of the

TABLE 2.—*Symptoms of Aniseikonia*

I.	Asthenopic symptoms
	Ocular discomfort (burning, itching, etc.)
	Ocular fatigue in close work and while watching moving objects (at movies, in driving, while watching games)
	Headaches of various types
	Photophobia
	General nervous fatigue or nervous tension, sleepiness, gastric symptoms, car and train sickness
II.	Impaired fusion and/or poor stereopsis
III.	Anomalous spatial localization

differential prismatic effect produced by glasses of markedly different strength, resulting in an artificial horizontal or vertical divergence which the wearer is unable to overcome. It appears that this effect may be only a secondary factor, the primary factor being the artificially created difference in the relative sizes of the ocular images. Unless there are other complicating factors, it is possible to correct anisometropia fully in every case provided the size difference is measured and corrected together with the refractive error.

5. He found photophobia in 46 per cent of his cases (Hughes, W. L.: Some Clinical Observations in Aniseikonia, Am. J. Ophth. **18**:715 [Aug.] 1935), which incidence agrees well with the figure of 54 per cent reported by E. H. Carleton and L. F. Madigan (Size and Shape of Ocular Images: II. Clinical Significance, Arch. Ophth. **7**:720 [May] 1932).

6. Hughes, W. L.: Clinical Aspects of Aniseikonia, Proc. Post-Grad. Course in Ophth., George Washington Univ. M. School **5**:116-145, 1940.

7. Carleton and Madigan,[5] noted general symptoms in 80 out of 96 cases and trouble in viewing moving objects in 64 out of 96 cases.

8. Hughes, W. L.: Aniseikonia in Emmetropia, Am. J. Ophth. **20**:887 (Sept.) 1937.

REPORT OF CASES

To illustrate what has been said so far, I shall briefly report some case histories. It is relatively rare that the symptoms are purely ocular; headaches [9] are frequently present and are sometimes the patient's only complaint.

CASE 1.—Mrs. C. B., a housewife, 32 years of age when examined on Aug. 10, 1939, complained of frontal and occipital headaches of many years' standing; the headaches had become more frequent in the past three years and were now present almost daily, sometimes accompanied by nausea. They were aggravated by close work and watching moving pictures. The family history disclosed nothing important. Repeated physical and ophthalmic examinations gave negative results. The eyes were externally normal, the media were clear, the pupils normal and the fundi showed no pathologic changes. Retinoscopy showed emmetropia in both eyes, with the visual acuity 20/15 in each. Subjectively, a + 0.25 D. sph. was accepted by each eye. Tests of the muscle balance disclosed 2 prism diopters of exophoria for distance and 6 prism diopters of exophoria for near vision. Examination for aniseikonia revealed that the right image was smaller by 2 per cent in the horizontal meridian. The patient was given the following prescription: right eye, plano lens ⌒ 2.00 per cent meridional magnification, axis 90; left eye, plano lens.

In the course of the two weeks following the first examination the headaches and nausea disappeared gradually, although at first the nausea seemed to be more severe. A reexamination gave essentially the same findings as the first examination, and the patient has been free from headaches since being fitted with iseikonic lenses.

This case is interesting in more than one respect. It shows, first of all, that headaches of ocular origin can be relieved by correcting the measured relative size difference and, furthermore, that headaches may be of ocular origin even if a careful routine examination does not reveal any ocular anomaly.[10]

Both physicians and laymen often ask whether migraine headaches are beneficially influenced by aniseikonic corrections. This question cannot be answered simply with "yes" or "no." First of all, not all prostrating, recurrent unilateral headaches accompanied by nausea are necessarily true migraine headaches. They are thus described only for want of a better diagnosis. On the other hand, true migraine headaches may appear in some forme fruste which masks their nature. It is advisable in all cases of unilateral headaches in which the usual methods

9. Carleton and Madigan,[5] found them in 75 of 96 cases, while R. E. Bannon (Headaches and Aniseikonia, Am. J. Optom. **17**:448 [Oct.] 1940) reported that they were a major symptom in 50 per cent and a minor symptom in 11 per cent of 635 cases.

10. Hughes [8] reported that 29 out of 43 patients with emmetropia measured for aniseikonia showed a clinically significant amount; 14 of these patients received complete relief by wearing aniseikonic corrections.

of treatment have been tried without avail to give the patient an examination for aniseikonia. Sometimes the patient obtains complete relief, as has been emphasized especially by Hughes.[11] When he does, the headaches were of ocular origin, since true migraine headaches could not be cured by aniseikonic lenses. However, even in cases of true migraine, the correction of a relative image size difference is sometimes beneficial. Aniseikonia may be one of the "trigger points" [12] releasing the attacks, and the interval between these attacks may be lengthened and their intensity decreased by the correction of the anomaly.

CASE 2.—O. A., a man aged 29, a factory worker, was first seen on May 27, 1939. He had never worn glasses but complained of severe eyestrain and headaches, especially in close work. The symptoms had become increasingly worse during the year previous to the examination. Ophthalmic examination gave negative results. The visual acuity was 20/20 in the right eye with a -6.75 D. sph. and 20/20 in the left eye with a $+1.00$ D. sph. $\bigcirc -1.37$ D. cyl., axis 155. Tests for aniseikonia showed the right ocular image to be smaller than the left by 14 per cent over all and by 4 per cent in the horizontal meridian. Tests of the muscle balance disclosed 8 to 12 prism diopters of exophoria and 3 prism diopters of left hyperphoria for distance and 12 to 18 prism diopters of exophoria and 3 prism diopters of left hyperphoria for near vision. There was double vision with the refractive correction alone; there was binocular single vision with the refractive and the aniseikonic correction. The following correction was given to the patient: right eye, -6.75 D. sph. $\bigcirc$ 14 per cent over-all magnification $\bigcirc$ 4 per cent meridional magnification, axis 90; left eye, $+1.00$ D. sph. $\bigcirc -1.37$ D. cyl., axis 155. In view of the high cost of the glasses this prescription was at first loaned to the patient in temporary form (fit-over lenses), but since it relieved all his symptoms completely, he acquired it in regular spectacle form and has been comfortable ever since.

In this case of high anisometropia it was possible to prescribe a full correction, which relieved the patient of his distressing symptoms without sacrificing his binocular vision. This patient showed an aniseikonia which was in the direction expected if the anisometropia were refractive: The ocular image of the myopic right eye was found to be considerably smaller than that of the left eye.

In extreme aniseikonia caused by unilateral aphakia, the result achieved with size lenses is even more impressive. If there are no other complicating factors it is always possible to restore binocular vision by correction of the measured size difference. However, owing to the enormous amount of aniseikonia, the glasses are cumbersome and their field qualities are poor. Since 1938 the Dartmouth Eye Institute has, therefore, resorted to the use of special contact lenses, with remarkably good result. By measuring the actual size difference present and computing contact lenses of appropriate curvature and thickness, it is possible

11. Hughes, W. L.: Aniseikonia, Am. J. Ophth. **19**:686 (Aug.) 1936.
12. Adams, F. D.: Personal communications to the author.

to correct the ametropia as well as the aniseikonia. While this matter is of great theoretic and practical interest, I mention it here only in passing, since an exhaustive paper on the subject is in preparation.

The amount of aniseikonia measured is often proportionate to the amount of anisometropia. But such a relation is not universal. One sometimes finds that the measured amount of aniseikonia is not in agreement with the amount which can be expected theoretically if a refractive anisometropia is present. This is shown in the following case:

CASE 3.—O. C. P., a 43 year old physician, had worn glasses for twenty-five years. He had recently noticed an unequal focus of the two eyes at the near point. Otherwise he had no complaints. Ophthalmic examination revealed no pathologic changes. Tests of the refraction and visual acuity showed the vision to be 20/20 in the right eye with a + 1.50 D. sph. and 20/20 in the left eye with a + 4.50 D. sph. For distance vision the patient had 1 prism diopter of esophoria and 2 prism diopters of left hyperphoria, and for near vision he had 5 prism diopters of esophoria and 2 prism diopters of left hyperphoria. With his refractive correction he had 100 per cent depth perception according to the graduated Keystone chart. In view of the large amount of anisometropia an examination for aniseikonia was suggested. This revealed that with refractive correction the image of the left eye (the more hyperopic one) showed a smaller ocular image than the right one. The measurements indicated that 0.75 per cent overall magnification had to be added to the correction for the left eye in order to equalize the images. No aniseikonic lenses were prescribed in this case.

The second group listed in table 2 refers to more objective symptoms. The number of instances in which it could be observed that stereopsis was considerably improved by the correction of even a small amount of aniseikonia argues in favor of the assumption that the difference in size of the ocular images is an obstacle to fusion. If one determines the stereopsis by means of some graduated chart while the patient wears his refractive correction, one may find little (10 or 20 per cent) or no stereopsis. As soon as the aniseikonia is corrected, the depth perception will improve more or less rapidly up to 80, 90 or even 100 per cent. If the aniseikonic correction is removed, the depth perception will remain good for a certain length of time but will finally return to its initial level. This prolonged effect of the aniseikonic correction on stereopsis is typical of fusional reactions and is, therefore, significant in explaining the effect of aniseikonic lenses.

CASE 4.—J. C. H., a high school student, was 18 years of age when first examined. He had worn glasses off and on for ten years. He had no subjective symptoms except for some general fatigue after close work. An ophthalmologic examination showed no pathologic changes in the eyes. Tests of the refraction and visual acuity showed the vision to be 20/15 in the right eye with a + 0.50 D. sph. and 20/15 in the left eye with a + 2.50 sph. ⊃ — 4.50 D. cyl., axis 30. Tests for aniseikonia showed the following correction to be needed, and it was added to the refractive lenses: right eye, 1.25 per cent meridional correction, axis

90; left eye, 3.00 per cent meridional correction, axis 180. With the refractive lenses the patient showed 2 prism diopters of esophoria for distance and 4 prism diopters of esophoria for near vision. With the refractive lenses alone, while the patient superimposed simple images in the stereoscope, he had no depth perception even for large objects. This behavior was checked independently by three members of the staff. After wearing the aniseikonic correction for three hours, the patient had 100 per cent depth perception with the graduated Keystone chart.

Anomalous relative and egocentric localization of objects in space, listed as group III in table 2, is closely related to the disturbances of stereopsis. The influence of over-all size differences and of differences in the principal meridians has been discussed in previous publications,[13] and exhaustive studies covering all other incongruities are being prepared for publication. I shall not discuss this subject in this paper, since to do so would lead too far into the complexities of physiologic optics. In the daily practice of the ophthalmologist, complaints about disturbances of spatial localization are not frequently met with. They are, however, of increasing importance in determining the aptitude of a person for the performance of certain tasks, for instance flying and landing an airplane.

A few words must be said about the relation of aniseikonia and heterophoria so far as their correction is concerned. Both disturbances result in fusional difficulties; the clinical picture is dominated in certain cases by heterophoria and in others by aniseikonia.[14] Only by trial can one tell whether one or the other, or both, have to be corrected. Many patients with heterophoria require a prismatic rather than an aniseikonic correction, but Carleton and Madigan [3] have reported a number of instances in which an aniseikonic correction was successfully substituted for the unsuccessful correction of heterophoria by prisms. These cases, however, must not be misconstrued as showing that the aniseikonic correction had eliminated the heterophoria. As is to be expected,[16] the heterophoria is almost always found to be of the same amount with and without the aniseikonic correction; but the improvement of the fusional conditions through the correction of the aniseikonia allows the patients to overcome their heterophoria with less subjective disturbance. In cases in which a reduction of the heterophoria has been noticed, one must assume that a strengthening of the fusion faculty

13. (*a*) Ames, A., Jr.; Ogle, K. N., and Gliddon, G. H.: Corresponding Retinal Points, the Horopter and Size and Shape of the Ocular Images, J. Optic. Soc. America **22**:538 (Oct.-Nov.) 1932. (*b*) Ogle, K. N.: Induced Size Effect: I. A New Phenomenon in Binocular Space Perception Associated with the Relative Sizes of the Images of the Two Eyes, Arch. Ophth. **20**:604 (Oct.) 1938.

14. Bannon, R. E., cited in footnote 9.

15. Footnote deleted.

16. Burian, H. M., in discussion on the papers of Lancaster, Berens and Loutfallah, Am. J. Ophth. **22**:639 (June) 1939.

enabled the patient to keep latent a larger amount of his heterophoria than previously.

An interesting case representative of the group of patients having both heterophoria and aniseikonia ends this short survey of the symptoms of aniseikonia:

CASE 5.—G. J. W., a 21 year old college student, complained of periodic crossed diplopia and ocular fatigue for all uses of the eyes and especially for close work. He had worn for two years before each eye a plano lens ⌒ 3.5 D. prism base in and had received two series of orthoptic exercises of three months' duration, neither measure giving relief. Tests of the refraction and visual acuity revealed the vision to be 20/15 in the right eye with a —0.25 D. sph. and 20/15 in the left eye with a —0.25 D. sph. For distance vision the patient had 16 prism diopters of exophoria, and for near vision he had 20 prism diopters of exophoria. Tests for aniseikonia disclosed that the right ocular image was smaller over all than the left by 3 per cent. Only the aniseikonic correction was given to the patient. Within a month he reported pronounced improvement; he had had fewer headaches, could read longer and had not once seen double. In order to insure that extraneous factors did not influence the patient's statements, three different corrections were given him experimentally without his knowledge; he returned them all stating that the only one which had really helped was the correction: right eye, plano lens ⌒ 3 per cent over-all magnification, and left eye, plano lens, which was given according to the aniseikonic measurements.

III. THE CLINICAL MEASUREMENT OF ANISEIKONIA

Aniseikonia is measured clinically with an instrument called an ophthalmo-eikonometer.[17] It consists chiefly of a head rest which allows an accurate adjustment of the position of the patient's eyes; in front of each eye are a number of cells designed to receive refractive lenses, size lenses, apertures and other accessories. The instrument allows one to measure not only aniseikonia but the heterophorias and the refraction by means of so-called stigmatoscopy.[18] The simpler type of this instrument, called an eikonometer (fig. 1), does not have this refractive device.

The principle of measuring aniseikonia is simple. After the head of the patient has been suitably and accurately adjusted in the instrument and the necessary refractive correction, if any, is properly placed in front of his eyes, the images received by the two eyes are partially dissociated by means of polarizing material; thus images are presented to the two eyes simultaneously which are seen in part monocularly and in part binocularly.

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17. (*a*) Ames, A., Jr.; Gliddon, G. H., and Ogle, K. N.: Size and Shape of Ocular Images: I. Methods of Determination and Physiologic Significance. Arch. Ophth. **7**:576 (April) 1932. (*b*) Ogle, K. N., and others: Repeatability of Eikonometer Measurements, ibid. **24**:1179 (Dec.) 1940.

18. Ames, A., Jr., and Gliddon, G. H.: Ocular Measurements, Tr. Sect. Ophth., A. M. A., 1928, pp. 102-176. Lancaster, W. B.: Stigmatoscopy, Tr. Am. Ophth. Soc. **32**:130, 1934.

The polarizing material which causes parts of the images to be seen with only one eye is attached directly to the slide. The fusion object on the slide, seen by both eyes, is not polarized. The patient is asked to compare the two ocular images, and the examiner is able to ascertain from his answers whether the image seen by one eye is of the same size as that seen by the other eye, and vice versa.

The target used most frequently for the measurement of aniseikonia consists of four pairs of arrows, located 4 degrees above, below, to the right and to the left of the center of a cross provided with a central circle (fig. 2). This pattern is projected on a large aluminized screen in such a way that the arrows bearing even numbers are polarized in

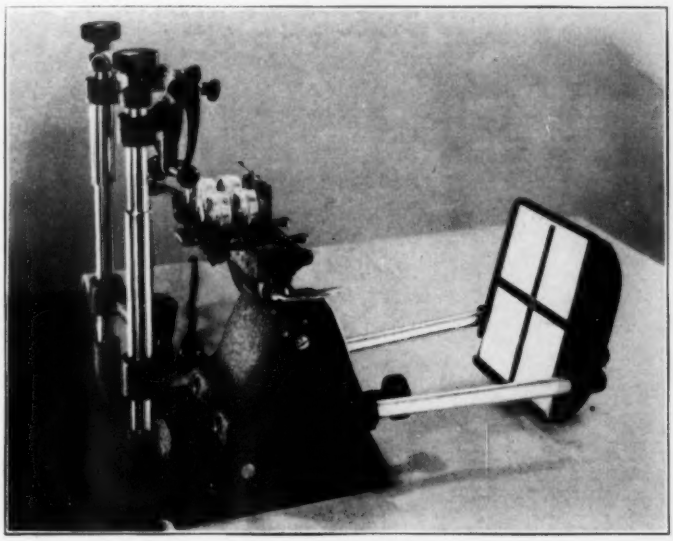


Fig. 1.—Eikonometer.

one direction and are seen by one eye (fig. 2*A*), while the arrows bearing odd numbers, which are polarized in the other direction, are seen by the other eye (fig. 2*B*). The cross and the central circle are seen binocularly. Under normal conditions the central circle exerts a sufficiently strong fusional stimulus when the eyes fixate the center or one pair of arrows so that binocular vision is maintained, although the largest part of the visual field of the two eyes is dissociated. Figure 2*C* shows the appearance of the target to the two eyes when all four pairs of arrows appear to be opposite each other; in this case there is no aniseikonia.

If there is a size difference, some of the arrows will not appear to be opposite each other, and in order to measure the amount of aniseikonia

special adjustable size units [19] are used in the instrument. These units allow one to change the size of the dioptric images either over all or in one meridian only without producing a measurable change in focus. The amount of relative magnification of the dioptric images necessary to equalize the two ocular images can be read from a scale on the rim of these lenses and expresses in per cent magnification the amount of the patient's aniseikonia. Per cent magnification means simply the ratio between the sizes of the two ocular images. The absolute size of these images is not known, but if it is found by measurement that the right ocular image is to the left one as 102 is to 100, the ratio is 1.02; i. e., the right ocular image is larger by 2 per cent.

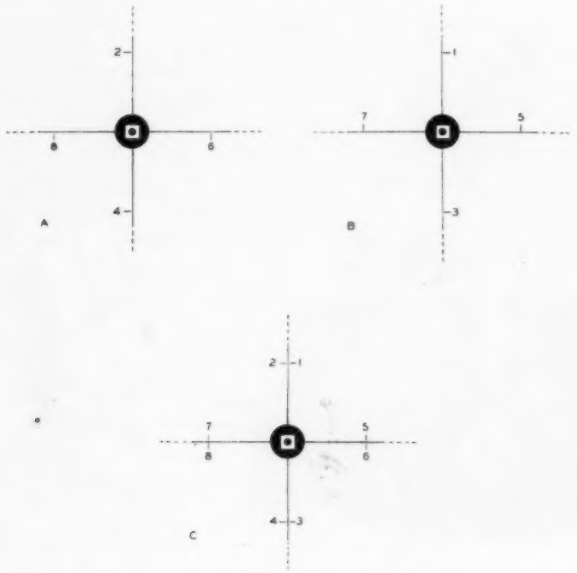


Fig. 2.—Target used in the measurement of aniseikonia. *A*, pattern as it appears to the left eye; *B*, pattern as it appears to the right eye; *C*, pattern as it would appear to both eyes if there were no aniseikonia.

Figure 3 shows how the target appears to the patient who has a meridional or over-all size difference. Is is assumed in the figure that the patient sees the odd numbers with the right eye and the even numbers with the left eye. In the first example (fig. 3 *A*), the upper vertical arrow, *1*, seen by the right eye, is higher than the corresponding arrow, *2*, seen by the left eye, while the lower vertical arrow, *3*, is below the corresponding arrow, *4*. The position of horizontal arrows *5* and *7* cor-

19. Ogle, K. N.: An Optical Unit for Obtaining Variable Magnification in Ophthalmic Use, J. Optic. Soc. America **32**:143 (March) 1942.

responds to that of arrows *6* and *8*. One concludes, therefore, that aniseikonia is present and that the ocular image of the right eye is larger in the vertical meridian only.[20] In the next example (fig. 3 *B*), while the positions of the vertical arrows, *1, 2,* and *3, 4,* coincide, arrow *5* is farther to the right than *6* and arrow *7* farther to the left than *8*; one concludes, therefore, that the ocular image of the right eye is larger in the horizontal meridian only. In the third example (fig. 3 *C*), all four arrows bearing odd numbers are displaced in such a way as to indicate that the right ocular image is relatively larger over all than the left (*1* above *2, 3* below *4, 5* to the right of *6* and *7* to the left of *8*). The last example (fig. 3 *D*) shows the opposite condition, the right ocular

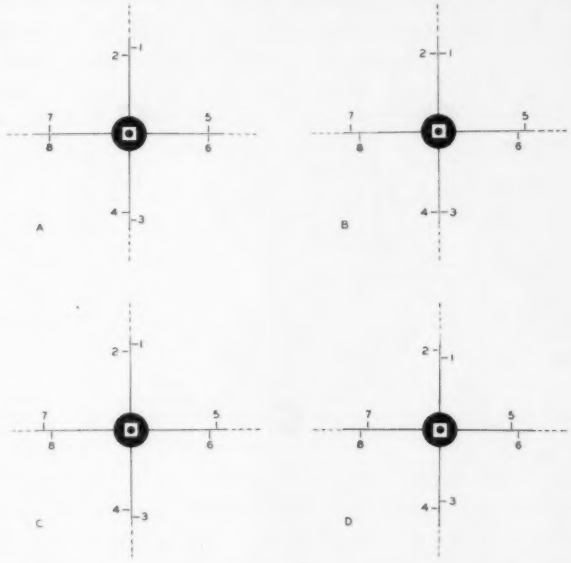


Fig. 3.—Schematic representation of the appearance of the eikonic target to patients with various types of aniseikonia. *A*, right image larger in the vertical meridian only; *B*, right image larger in the horizontal meridian only; *C*, right image larger overall; *D*, right image smaller overall.

image being relatively smaller over all than the left (*1* below *2, 3* above *4, 5* to the left of *6* and *7* to the right of *8*).

Although the fusional stimuli offered by the target are adequate for the measurement of aniseikonia, they are not strong enough to keep the heterophorias, if they are large, entirely latent. The result is that a certain amount of esophoria, exophoria or hyperphoria becomes mani-

20. The meridians and axes in aniseikonia are designated analogously to the meridians and axes of astigmatism: A size lens at axis 90 magnifies the ocular image in the horizontal meridian.

fest in spite of the presence of a fusion stimulus. This condition has been designated as "fixation disparity." [13a] It is characterized by an equal vertical or horizontal displacement of the odd-numbered arrows. A fixation disparity may be present simultaneously with aniseikonia.

Figure 4 shows examples of this condition. If vertical arrows *1* and *3* are displaced upward equally, relative to the corresponding arrows, *2* and *4* (fig. 4 *A*), one concludes that there is a vertical fixation disparity, indicating that a left hyperphoria, but no aniseikonia, may be present. If horizontal arrows *5* and *7* are displaced equally to the right, relative to arrows *6* and *8* (fig. 4 *B*), there is a fixation disparity pos-

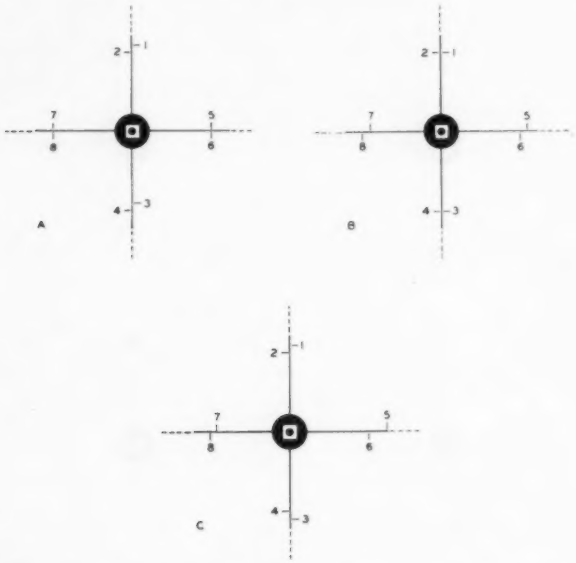


Fig. 4.—Schematic appearance of the eikonic target to patients with fixation disparity. *A*, vertical fixation disparity; *B*, horizontal fixation disparity; *C*, combination of aniseikonia (right image larger overall) with horizontal fixation disparity.

sibly indicative of an esophoria, but no aniseikonia. Finally, figure 4 *C* shows the combination of aniseikonia (in this case a relative over-all increase of the right ocular image) with an esofixation disparity (expressed in a shift of horizontal arrows *5* and *7* to the right).

For the measurement of aniseikonia in near vision (40 cm.),[22] a negative photographic plate is used that shows the same pattern as that projected on the screen for distance vision. This plate is illuminated

21. Footnote deleted.

22. Ogle and others.[17b]

from behind, and pieces of polarizing material are placed over the arrows so that the arrows bearing the odd and the even numbers are again seen only by the right eye or the left.

IV. SIZE LENSES AND THE CORRECTION OF ANISEIKONIA [23]

In order to correct an aniseikonia, one usually increases the size of the smaller image.

The relative size of the dioptric images can be modified by changing either the distance of the corrective lenses from the apex of the cornea or the thickness and curvature of the lenses themselves. Obviously, the first alternative is impractical. One must make use of the thickness and curvature of the lenses to introduce a change in magnification.

The image of an object seen through a plane parallel glass plate is displaced toward the plate by a distance roughly equal to one third of the thickness of the plate. The decreased distance of the image from

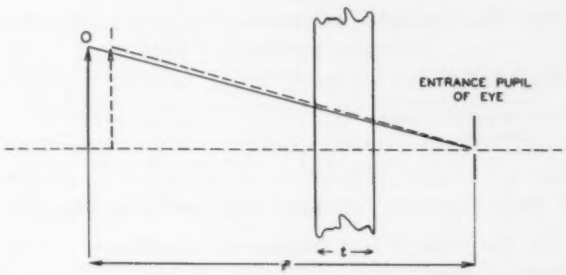


Fig. 5.—Magnification through a plane parallel glass plate.

the eye as compared with the object distance produces an angular magnification. This magnification is the greater the thicker the plate, but decreases as the distance of the object from the glass increases (fig. 5).

The magnification produced by a plane parallel glass plate can be modified by introducing a curvature. The magnification depends on the refractive power of the front surface and the thickness of the lens. The magnitude of magnification is the greater the more curved the front surface and the thicker the plate.

The so-called size lenses make use of this principle to change the relative sizes of the dioptric images. They are so designed that the refractive power of the surface toward the object is offset by the refractive power of the surface of the lens toward the eye, so that the image of the object is situated at the location of the object itself. In other words, when such lenses are placed before an eye they do not cause it to become apparently hyperopic or myopic. They can be ground as over-all size

23. Ogle, K. N.: The Correction of Aniseikonia with Ophthalmic Lenses, J. Optic. Soc. America **26**:323 (Aug.) 1936.

lenses, having the same magnification in all meridians, or as meridional size lenses, having a specified magnification in one meridian but no magnification in the meridian at right angles to it. The latter size lenses introduce or correct a size difference in one meridian only and are, therefore, called meridional size lenses.

Table 3 shows an example of a size lens introducing a magnification of 4 per cent for the visual distance of 75 cm.

In most cases it is possible to incorporate into size lenses, in addition to the magnification, a refractive correction and, if necessary, prisms, even in bifocals. Such lenses are called iseikonic lenses.

At times a temporary aniseikonic correction in the form of a fit-over has to be added to the patient's refractive correction. In some complicated cases this may amount to a number of lenses in front of the patient's eyes, but ordinarily it is possible to give the patient a pair of normal-looking spectacles.

TABLE 3.—*Example of a Size Lens Introducing 1.04 or 4 per Cent Magnification for a Visual Distance of 75 Cm.*

Front surface power	+11.82 D.
Back surface power	—12.16 D.
Thickness	4.7 mm.

V. THE CLINICAL SIGNIFICANCE OF ANISEIKONIA

To sum up the clinical significance of aniseikonia: One is able to relieve patients of distressing symptoms by means of aniseikonic corrections when all other attempts to cure them have failed; one is able to prescribe full anisometropic corrections, even for unilateral aphakia, thus giving patients the benefit of full binocular vision without creating insufferable symptoms, and, finally, one can correct anomalies of spatial localization by means of iseikonic lenses. It is impossible to care for all patients with eyestrain without determining for some of them the presence and the amount of aniseikonia.

This statement raises the question, first of all: How can one tell whether or not a patient has a significant amount of aniseikonia? The answer can be determined only by actual measurement; for the time being there is no simple test which would exclude the presence of aniseikonia. This situation is unfortunate for a number of reasons. The present equipment is expensive; the examination is long and must be made by a clinician experienced in aniseikonia. It is not probable that aniseikonic examinations will soon become an office routine. However, a number of centers are now established in various parts of the country, and it should be easier now than before to refer patients to one of them. The selection of patients is a relatively simple matter. If a patient does not obtain relief from his symptoms by correction of

his refractive error and his muscular imbalance and if other physical causes have been excluded by competent physical and neurologic examinations, there is good reason to believe that an aniseikonic correction may benefit him. This is especially true if the symptoms appear in some of the characteristic combinations previously mentioned.

An examination for aniseikonia is at this time comparable to a laboratory test for syphilis. One may suspect from the patient's history a syphilitic origin of a paresis of the ocular muscles, but one has to await the result of the blood test before one can be sure of the causation. Similarly, an examination for aniseikonia has to be made before one can tell whether a significant amount is present. It has been frequently suggested that occlusion of one eye might be used as a screening test for aniseikonia. This test, however, is not reliable. It is difficult and requires a good deal of time for interruption of the binocular coordination. Furthermore, aniseikonia is only one of the binocular anomalies which may cause difficulties, and the test, therefore, is not specific.

There are certain patients whose ocular conditions do not permit an eikonometric examination. They comprise for the most part patients with heterotropia as well as all those whose fusion faculty is insufficient to enable them to see the eikonic target binocularly and singly. For such patients special instrumentation has to be used which at present is not available for routine examinations. Also, the corrected vision must be sufficient to allow the patient to see the target with adequate clarity.

The question is often asked: How frequent is aniseikonia? As has been pointed out before, aniseikonia is as universal as the errors of refraction or the heterophorias; but a correction for aniseikonia is not warranted unless its amount is clinically significant.

I must define more clearly what is meant by a "clinically significant" amount. As with all ocular measurements, it depends largely on the patient, his occupation, his symptoms, his tolerance and his sensitivity, whether the measured amount of aniseikonia is significant or not. In certain cases a hyperopia of +0.75 or +1.00 D. cannot be tolerated by the patient without correction; in others +2.00 or +3.00 D. causes no distress. Hyperphoria of 4 or 6 prism diopters is usually significant, but I have seen patients with as much as 16 or 20 prism diopters of hyperphoria who have no discomfort whatever, although they have normal binocular vision. Analogously, patients with a high sensitivity to and/or a low tolerance for relative image size differences are more readily affected by a much smaller amount of aniseikonia than patients with a high tolerance and/or a low sensitivity.

The general experience is that a size difference of 1 per cent is significant. It is important to emphasize this fact; in a sense it is the

crux of the practical aniseikonic problem that such an apparently small amount of size difference is capable of producing symptoms. The usual amount found in clinical cases varies from 1 to 2 per cent; an aniseikonia of over 3 per cent as a rule entails a definite impairment of binocular vision; more than 5 per cent is found only in cases in which binocular vision is very imperfect or entirely absent under the normal conditions of seeing.

The curves and figures reproduced in figure 6 and table 4 are instructive as regards both the incidence of aniseikonia and its clinical significance. Figure 6 shows that 93 per cent of the 107 flight cadets

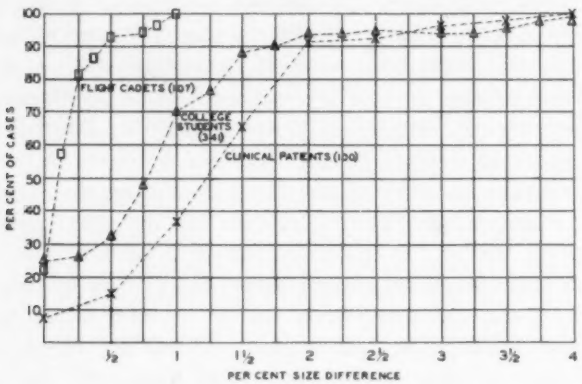


Fig. 6.—Incidence of aniseikonia in various populations.

TABLE 4.—*Average Amount of Aniseikonia in Three Selected Groups*

	Flight Cadets, per Cent	Students, per Cent	Patients, per Cent
Aniseikonia of 1% or less	100	70	36
Aniseikonia of 1 to 2%	0	23	55
Aniseikonia of over 2%	0	7	9

measured for aniseikonia at the United States Naval Air Station at Pensacola, Fla., measured 0.50 per cent or less and that all of them showed 1 per cent or less. In a group of 341 students of one class of Dartmouth College, 33 per cent showed 0.50 per cent or less. Seventy per cent measured 1 per cent or less, 23 per cent showed 1 to 2 per cent and 7 per cent had over 2 per cent.

The distribution is quite different for 100 consecutive clinical patients whose measurements were recorded for comparison. Only 16 per cent showed 0.50 per cent or less; 36 per cent measured 1 per cent or less, the bulk (55 per cent) measured between 1 and 2 per cent and 9 per cent showed more than 2 per cent. The figures for these three groups clearly

show that the average amount in the highly selected group of flyers is much lower than that in essentially normal but unselected students of the same age group and still lower than that in a group of persons with ocular complaints. I consider these figures to be convincing evidence for the role played by aniseikonia as a factor in the production of ocular symptoms.

There is a striking agreement in the statistics which have been published by various authors about the results achieved with iseikonic lenses: In all of them the percentage of beneficial results is put at about 70. In judging this figure one must keep in mind that a great number of patients are sent by the referring physicians for aniseikonic examination only as a last resort. A fair picture of the ratio between successful and unsuccessful results will not be obtained until statistics are worked out in which only those cases are taken into account in which the patient can be classified as being "definitely aniseikonic." At present numerous cases unsuitable for statistical purposes are necessarily included.

It is of interest to note that the aniseikonic measurements of patients whose condition was followed over a number of years showed a remarkable constancy.[17b] This obviously points to the fact that the measurements are not haphazard results but are the expression of an objective condition, being comparable in this respect to the measurements of refractive errors.

At the same time this constancy makes it improbable that the favorable results obtained from aniseikonic corrections are due to psychologic factors, as is sometimes claimed. It is typical of conditions which are largely functional, and which can therefore be influenced by psychologic factors, that the measurements obtained are erratic. Stable measurements point toward an organic basis of the trouble.

One may or may not agree with the theoretic conclusions reached in the research on aniseikonia. One may or may not believe in some aspects of its clinical applications. It is undeniable, however, that an ever increasing number of patients who are unable to obtain comfort by any other means are relieved of distressing symptoms by the wearing of iseikonic corrections. To me, as a physician, this is convincing evidence of the practical value of aniseikonia.

Dartmouth Eye Institute.

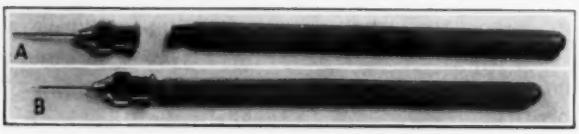
Clinical Notes

INSTRUMENT FOR REMOVAL OF FOREIGN BODY FROM CORNEA

First Lieutenant Glen F. Harding
MEDICAL CORPS, ARMY OF THE UNITED STATES

The instrument to be described solves the need for an inexpensive, replaceable and easily sterilized instrument.

The use of a regular stainless steel hypodermic needle of any gage and with any type of point desired by the operator is possible. Should a rounded point be desired, the needle can be ground down with a white stone.



The instrument described: *A*, detached; *B*, ready for use.

The use of a hollowed, sharp needle point tends to create a smaller field of trauma, and any rusted infiltration of the cornea can be readily removed for rapid healing.

I use a stainless steel 25 gage needle, sterilizing it by boiling for ten minutes. If the point is damaged it is replaced with a new one.

The handle of the instrument is constructed of hollow, chrome-plated brass. The tapered brass needle-holding tip is ground carefully to produce a tight fit.

The placement of the needle in and its removal from the handle are easily accomplished by means of a slight twisting-pressure motion.

A locking arrangement to hold a Luer-Loc type of needle in the handle was found unnecessary, as the needle has never loosened in use.

Correspondence

PARTICLES OF STEEL WITHIN EYE

To the Editor:—The article by Dr. Francis D. Gulliver, "Particles of Steel Within the Globe of the Eye," in the November issue (ARCH. OPHTH. **28:** 896, 1942), contains much with which I disagree.

His nomenclature of the anatomy of the eye is not in accordance with accepted usage. He refers to the anterior chamber as all the space in the anterior segment of the eye, making no differentiation between the anterior and the posterior with the iris as the limiting structure between these two spaces. The posterior chamber according to him is what is invariably referred to as the vitreous chamber. He further states that the structure of the vitreous is solid or semisolid, when in truth it is viscous.

One wonders what the sources of his reported 1,800 cases were when he states that the particle in less than 0.5 per cent was nonmagnetic and that the contact of metal in machines rarely causes intraocular penetration of a foreign body. Industrial ophthalmologic practice in a metropolis must indeed be different from that in an industrial center.

I have had a wide experience in this branch of ophthalmology in Pittsburgh in the past forty-five years. One corporation for which I served as ophthalmic surgeon employs 40,000 men, includes departments making all sizes of iron and steel products, from nails to armor plate, and operates its own ore and coal mines and limestone quarries. In the variety of man power employed, eyes too frequently are penetrated by copper from percussion caps and pieces of stone and coal in premature blasts. In the laboratories and by-product departments, glass retorts and tubes explode with great velocity, driving splinters of glass into the eyes. Further, many eyes are injured by particles of steel flying from power-driven lathes, drill presses, punches and shears.

As a matter of course all heavy industry has efficient safety organization, part of the routine precautions being to inspect daily for mushroomed tools, which when found are redressed or scrapped.

It is true that accidents caused by defective tools occur all too frequently and happen usually in small machine shops or garages.

I deplore the use of the giant magnet for drawing magnetic particles from the vitreous through the structures in the anterior part of the eye. In using such a cumbersome aid as the giant magnet, he who can direct the foreign body through the zonula and not injure ciliary body, iris or lens is expert indeed.

It must be remembered that a steel or iron particle through which a magnetic current has been passed also becomes a magnet, with a positive and a negative pole. The positive pole of the giant magnet will attract the positive pole of the particle, and a foreign body 2 or 3 mm. long may penetrate to the nucleus of the lens. I saw this happen in the case of a young colleague.

When properly performed, extraction through a scleral incision is practically without risk. After the location and the size of the foreign

body are known, a sliding conjunctival flap baring the sclera is made and at a point nearest to the foreign body the sclera is incised, not by plunging of a knife into the vitreous but by successive dissecting strokes to expose the choroid, which is then gently incised. The size of the scleral opening depends on the size of the artefact. The cone tip of the magnet is then applied, and only then should the current be turned on.

As I pointed out (*Tr. Am. Ophth. Soc.* **37:** 405, 1939), if 220 volts of current is passed through the coil of the magnet, the magnetic field is doubled, and I have never failed to extract a magnetic foreign body with the hand magnet. I discarded the use of the giant magnet many years ago.

The outstanding fear among ophthalmic surgeons is detachment of the retina. Long before the advent of the operations now in vogue for detachment of the retina, I treated this lesion by draining the subretinal fluid through small scleral punctures and then applying pure phenol in the openings. By doing this after the foreign body has been recovered, one sets up a localized plastic inflammation which makes the choroid and the retina adhere to the sclera, and the retina remains adherent.

I have kept myself posted on the comparative results obtained with both routes of extraction, but I cannot recall having read of extreme and total loss of sight occurring in a large percentage of cases after transscleral extraction, as reported by the essayist. Such loss of sight has most emphatically not occurred in my experience, which embraces slightly more than 800 cases.

EDWARD STIEREN, M.D., Pittsburgh.

626 Union Trust Building.

News and Notes

EDITED BY DR. W. L. BENEDICT

SOCIETY NEWS

Reading Eye, Ear, Nose and Throat Society.—The fifteenth meeting was held Nov. 18, 1942. It was addressed by Dr. Walter I. Lillie on the subject "Vascular Changes in Hypertensive Disease." Dr. Lillie brought out the importance of studying the second and third branches of the vessels for beginning spasticity during cycloplegia. He presented conclusive statistics for the life expectancy of persons with the various forms of hypertensive disease.

Obituaries

EDWARD JACKSON, M.D.
1856–1942

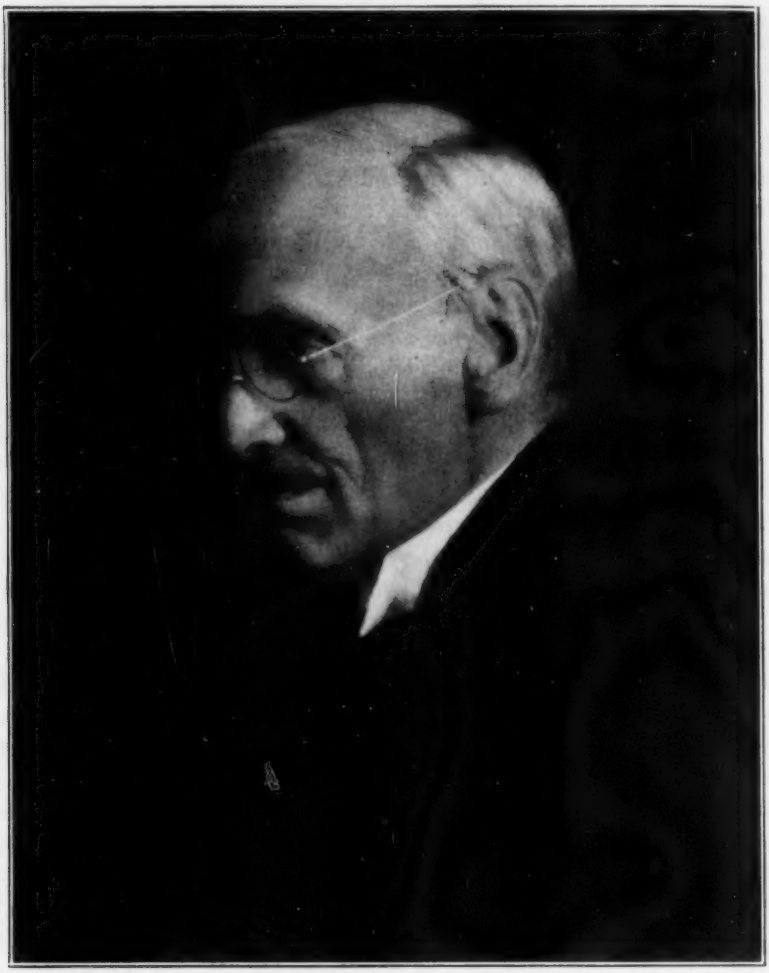
Dr. Edward Jackson died in Denver Oct. 29, 1942, at the age of 86. Born in West Goshen, Chester County, Pa., the son of Holliday and Emily (Hoopes) Jackson, he was graduated in 1874 from Union College, where he was an engineering student, and received his Doctor of Medicine degree from the University of Pennsylvania four years later. He practiced in West Chester from 1878 to 1884 and then returned to Philadelphia to devote himself to ophthalmology. His success in this specialty was prompt and his progress rapid, so that he became professor of diseases of the eye at the Philadelphia Polyclinic Hospital in 1888 and surgeon at the Wills Hospital in 1890.

Dr. de Schweinitz, in his excellent introduction to "Contributions to Ophthalmic Science Dedicated to Dr. Edward Jackson," stated that "Edward Jackson was the prime mover in starting the ophthalmic section of the College of Physicians of Philadelphia in 1890 and from the first he strove to influence the members to present their best work, and have it suitably prepared for publication." His regular appearance at all ophthalmologic meetings without regard to travel or season of the year showed his interest and devotion to furthering the standards of ophthalmology. His presentation of papers or taking part in the discussion always enlisted the closest attention on the part of the audience. Gifted with facility, he expressed himself precisely and clearly. He took an active part in the special societies and associations and became chairman of the Section on Ophthalmology of the American Medical Association in 1894, president of the American Academy of Ophthalmology and Otolaryngology in 1903 and president of the American Ophthalmological Society in 1912.

After his removal to Denver Dr. Jackson continued his teaching career. He became professor of ophthalmology at the University of Colorado in 1905 and occupied this position until his retirement in 1921. Then, far from retiring, he devoted his energies to postgraduate teaching, a subject in which he was always particularly interested, and founded the Denver postgraduate course, whose success soon led to the formation of similar courses in many parts of the United States. Dr. W. H. Crisp informed me that the three day course of conferences of the American Academy of Ophthalmology and Otolaryngology, begun in 1921, was inspired by a paper delivered in 1917 by Dr. Jackson before that society,

under the title "Defects in Education for Ophthalmic Practice," from which the following paragraph is taken (*Am. J. Ophth.* **1:** 486, 1918):

An organization like this could arrange to give, just before its annual meeting, a week of intensive training on the microscopic diagnosis of intraocular tumors,



EDWARD JACKSON, M.D.
1856–1942

under three or four of its members who have given special attention to ocular pathology. Or, to make the best use of the time with the least strain of any one set of powers, this might be combined with a similar course on experimental optics, or the minute anatomy of the eye with reference to operations on the anterior segment, or the location of foreign bodies. Such courses should be put on a basis

of fees that would compensate the instructors, and provide the necessary material or equipment. Similar courses could be arranged by local ophthalmologic societies for the benefit of their own members, and to suit their convenience.

Perhaps his greatest contribution to ophthalmology in this country was literary, and no one was as industrious a writer; books, monographs, special chapters and an endless array of publications carried his name as author. He established in 1904 the "Ophthalmic Yearbook" and was the chief editor of the *American Journal of Ophthalmology* from 1918 to 1928. Dr. de Schweinitz spoke particularly of the influence exerted by his initialed editorials, which fortunately were kept up to the time of his death.

His mathematical training and early interest in physiologic optics attracted him to the problems of refraction. He published important papers on skiascopy, the designation of prisms by their angular deviation, the necessity of full correction of myopia, subjective methods to determine astigmatism and standardization of test types. His name will always be associated with the cross cylinder. He devised an operation for transplanting the superior rectus muscle in the treatment of paralysis of the superior oblique. Investigations on tuberculosis of the retina were undertaken in association with Dr. W. C. Finnoff, and he early realized the importance of ophthalmoscopic examination in recognition of the early changes in the finer vessels of the retina.

Dr. Jackson was the recipient of two outstanding awards in American ophthalmology, namely, the Howe medal of the American Ophthalmological Society and the Howe research medal of the Section on Ophthalmology, American Medical Association. In 1925 he delivered the Jacob Lambert Lecture on "The Prevention of Blindness by Good Lighting" and received the Leslie Dana medal.

By the death of Edward Jackson, ophthalmology has suffered a great loss and an outstanding personality. A great teacher, a man of great industry, always genial and friendly, he spared no effort to instruct and encourage. It is no exaggeration to state that he devoted his life to the education of the American ophthalmologist and thereby served ophthalmology. He had a warm personality, combined with a sincere and robust character. In his long life, he achieved much, and his death leaves a serious gap, but his devoted service to American ophthalmology will long remain an inspiring example.

ARNOLD KNAPP.

Death has taken one of the outstanding pioneers in the movement for the prevention of blindness, Dr. Edward Jackson. He reached the ripe age of 86 and was active to the end of a career that was of the greatest service to mankind.

Dr. Jackson's efforts to conserve vision extended over a period of sixty years. In addition to being a distinguished ophthalmologist, he was a trail blazer in the lay movement for the protection of eyesight. In recognition of his achievements in this field, he received the first award of the Leslie Dana gold medal, established in 1925.

His contributions to medicine as teacher, writer and practitioner—were immense. He was surgeon to the Wills Eye Hospital in Philadelphia for several years, professor emeritus of ophthalmology in the University of Colorado, consulting editor of the *American Journal of Ophthalmology* and former president of all leading ophthalmologic societies.

A modest and wise man, Dr. Jackson was long known affectionately as "the dean of American ophthalmologists," and his name was respected in scientific circles throughout the world. Men of his stature and attainments are rare and are difficult to replace.

The Board of Directors of the National Society for the Prevention of Blindness notes the great contributions which he made to humanity and requests that a minute of this appreciation be spread on the official records and a copy sent to Dr. Jackson's family.

NATIONAL SOCIETY FOR THE PREVENTION OF BLINDNESS.

FRANK W. MARLOW, M.D.

1858–1942

Dr. Frank W. Marlow died in Syracuse, N. Y., on Oct. 5, 1942, at the age of 84. Born in Abington, England, he passed most of his youth in Wantage, Berkshire, 26 miles from Oxford, where his father was manager of the bank. After attending King Alfred School, in Wantage, he received his medical education at St. Thomas' Hospital, at a time when major surgical procedures were performed under a phenol spray. At St. Thomas' he met Mr. J. B. Lawford, who remained his close friend through life and who influenced him to go into ophthalmology. Dr. Marlow was under Mr. Edward Nettleship at St. Thomas' and later served on his staff at Moorfields.

At the suggestion of Dr. Clifford Mercer, who at that time was doing postgraduate work in pediatrics in London, Dr. Marlow came to this country in 1884 and settled in Syracuse, N. Y., where he began a long and successful career as an ophthalmologist. He was most painstaking and meticulous in all his work and, with his excellent training, rapidly acquired a large and devoted clientele and became the outstanding authority in his field in central New York state. His son, Dr. S. B. Marlow, told me:

> The speed with which his operation for cataract was performed must have been influenced by his early training in the precocaine days. The section was made, the knife seemingly thrown anywhere, the iridectomy done and the lens expressed in a twinkling. The results were exceptionally good: little reaction and few accidents. He never used a bandage in a case of cataract; at least I never saw him do so. For glaucoma, when iridotasis was advocated he took it up and used it almost exclusively, with uniformly good results.

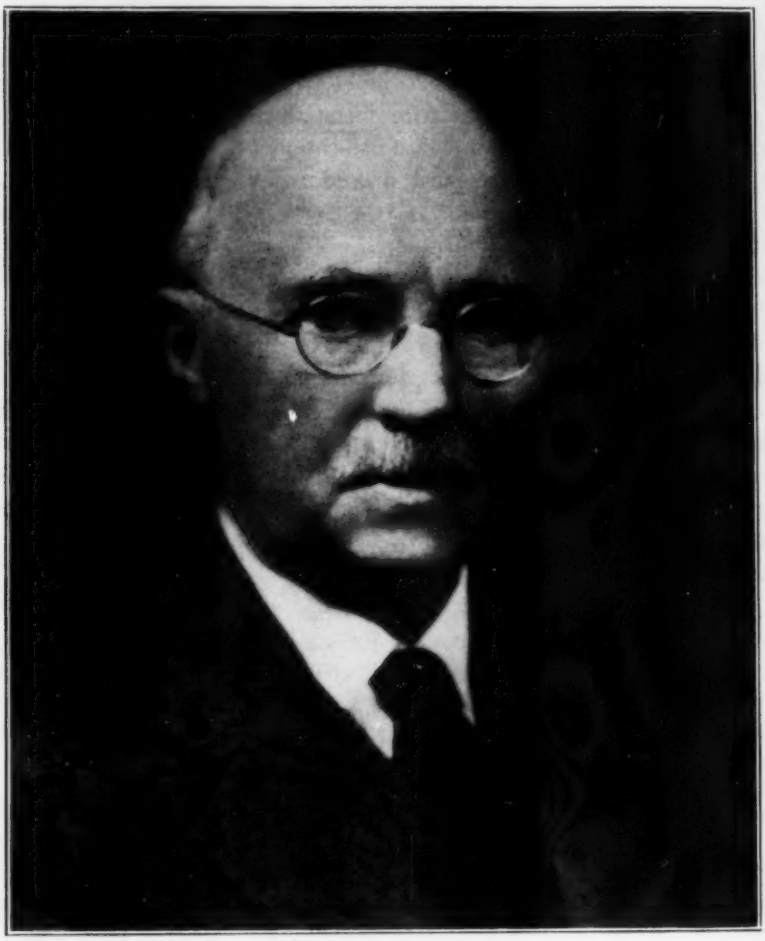
His early training impressed on him the importance of ophthalmoscopic examination, but his principal interest lay in motor anomalies.

He early became associated with Syracuse University College of Medicine, taught as professor of ophthalmology for forty years and was largely instrumental in the foundation of the Syracuse Free Dispensary and the Syracuse Memorial Hospital. He was an active member in the local medical societies and was an important factor in establishing high ethical standards in medicine in Syracuse. Dr. Marlow was an early member of the Ophthalmological Society of the United Kingdom and of the American Ophthalmological Society.

His outside interests lay in music and photography. He was fond of good music, was an accomplished violinist and knew a great deal

about violins and their history. His work in photography was outstanding, and he was proficient in all the steps of this art.

Of a retiring disposition, he found speaking in public and reading papers at medical meetings an ordeal to be dreaded and avoided. Nevertheless, a number of valuable articles have appeared from his pen, written



FRANK W. MARLOW, M.D.
1858–1942

in clear and concise English, many on his favorite subject of muscular anomalies, for which the prolonged occlusion test stands out as a real contribution, of permanent value in diagnosis.

He is survived by his widow, Mrs. Laura Bisset Mills Marlow, two daughters and three sons.

ARNOLD KNAPP.

LUTHER CROUSE PETER, M.D.

1869–1942

Dr. Luther C. Peter, professor emeritus of ophthalmology in the Graduate School of Medicine of the University of Pennsylvania since 1940, died Nov. 12, 1942, at the age of 73 years, in the Graduate Hospital, from complications following an operation for an impacted gallstone in the common duct.

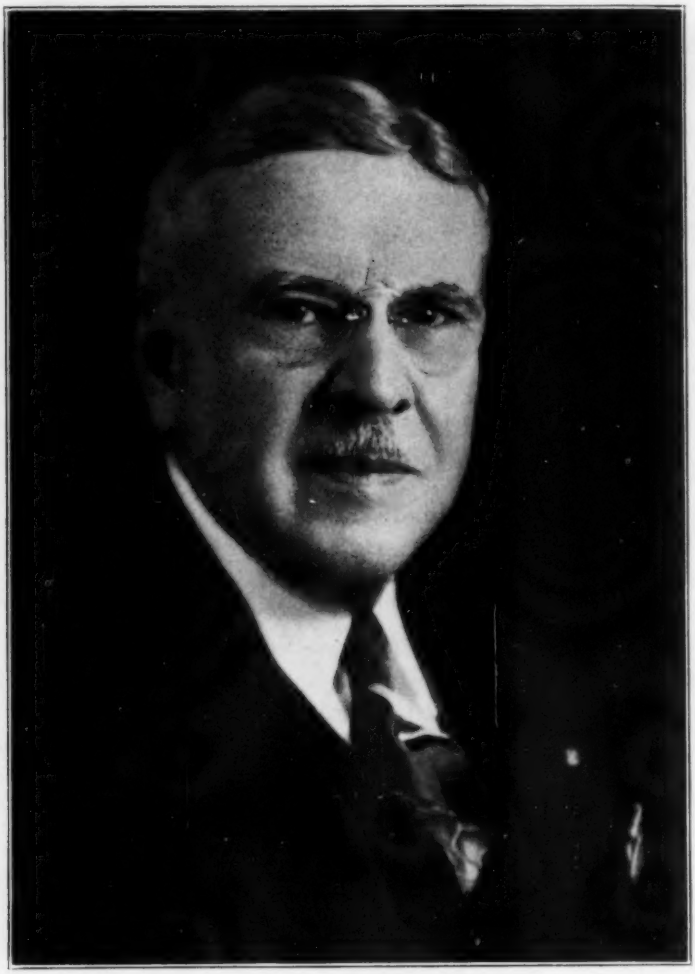
Dr. Peter, the son of Rev. Jacob and Harriet Jane (Crouse) Peter, was born in St. Clairsville, Pa., Feb. 14, 1869. He received his elementary education in the schools at Manheim, Pa., attended Susquehanna University until 1888 and was graduated from Gettysburg College in 1891, where he did postgraduate work until 1892, at which time he received a Master of Arts degree. He then entered the University of Pennsylvania and was graduated with the degree of Doctor of Medicine in 1894. In 1926 Gettysburg College awarded him a Doctor of Science degree, and Susquehanna University awarded him a similar degree in 1934; in 1933 he received a Doctor of Laws degree from Gettysburg College. The Phi Beta Kappa chapter of Susquehanna University elected him to postgraduate membership in 1925.

He married Carrie Chrystine Moser, who survives him, on June 20, 1916. They had no children.

Dr. Peter was a Lutheran in active membership as a vestryman at St. John's Church in Rosemont, Pa.; he was, at one time, active in the shrine and greatly interested in Masonry. A Republican of firm convictions, Dr. Peter was at all times keenly interested in municipal and national politics and had an extensive personal and corresponding acquaintanceship with many state and national leaders of that party. He was an omnivorous reader, biography, travel material and detective and mystery fiction claiming his attention, as well as medical literature. At the outset of the present war he and Mrs. Peter had plans for an extensive trip through the Orient, having traveled abroad numerous times and visited Alaska and Mexico.

While serving in the neurologic clinics of the old Orthopedic Hospital, he became interested in the ophthalmologic aspects of this specialty and started working with Dr. Wendell Reber, hoping to learn more about the fundus of the eye and the ocular manifestations of disease of the central nervous system. It was a natural sequence of events that he should detach himself more and more from general medicine and from his interests in neurology, so that in 1908 he was working entirely in ophthalmology. In 1910 he was appointed assistant professor of

ophthalmology at the Philadelphia Polyclinic Hospital and School for Graduate Medicine; in 1918, associate professor of ophthalmology at the same institution, which was at that time absorbed by the University of Pennsylvania as the Graduate School of Medicine of the university,



LUTHER CROUSE PETER, M.D.
1869–1942

and, finally, in 1919, professor of ophthalmology. In 1930 he resigned from the faculty of Temple University School of Medicine as professor of ophthalmology, having served in that capacity from 1917.

He was a member of the American Board of Ophthalmology from 1929 to 1937, its president from 1935 to 1937, and secretary of the

American Academy of Ophthalmology and Otolaryngology from 1919 to 1926, its president in 1928-1929. He was elected to the American Ophthalmological Society in 1922, to the Philadelphia College of Physicians in 1917 and to fellowship in the American College of Surgeons in 1920. Dr. Peter was secretary of the International Congress of Ophthalmology held in Washington, D. C., in 1922 and was guest lecturer at the Oxford Congress (England) in July 1920, his subject being "Perimetry," and again in July 1932, his subject then being "The Treatment of Nonparalytic Squint."

Many articles were contributed by him to ophthalmologic literature on perimetry, disturbances of the extraocular muscles, neuro-ophthalmology, the surgical aspects of cataract and of glaucoma and, more recently, the treatment of retinal separation. His book "The Principles and Practice of Perimetry" appeared in four editions, and in 1940 "The Extra-Ocular Muscles" had its third edition. While actively engaged in practice, he was on the hospital staff as ophthalmologist of the Graduate Hospital of the University of Pennsylvania, Rush Hospital for Consumption and Allied Diseases, Friends Hospital for mental and nervous diseases and the Roxborough Memorial Hospital.

During Dr. Peter's active years of undergraduate and postgraduate instruction in ophthalmology, he was, without doubt, a definite factor in the ophthalmologic training of the many students who came in contact with him. It is certain that he left with them an incentive and stimulus for hard work and for the detailed investigation of those problems or situations which were certain to appear in their chosen specialty. This influence in ophthalmology will continue for many years.

It is proper and fitting that as Dr. Peter's senior assistant for the past fifteen years I gratefully and sincerely acknowledge here the many opportunities he made possible to me for the study and practice of ophthalmology.

EDMUND B. SPAETH.

Abstracts from Current Literature

EDITED BY DR. WILLIAM ZENTMAYER

Anatomy and Embryology

THE INSERTIONS OF THE LEVATOR PALPEBRAE MUSCLE. H. R. HILDRETH, Am. J. Ophth. **24:** 749 (July) 1941.

Hildreth gives the following summary:

"In brief, the levator muscle is connected to the upper lid chiefly by means of its tendon. The tendon is a broad, dense, connective-tissue layer. The terminal fibers of the tendon insert into the lower anterior surface of the tarsus and also into the skin. Underneath the tendon lies Müller's smooth-muscle layer. This delicate tissue arises from the belly of the levator muscle as a lamella separate from the overlying tendon. It inserts directly into the upper border of the tarsus. Conjunctiva lines the under surface of the tarsus and Müller's muscle.

"Ptosis of the upper lid caused by partial paralysis of the levator muscle can be corrected by increasing the power of the levator muscle. A satisfactory procedure for doing this is advancement of the levator tendon through a skin incision. The broad cut end of the tendon should be sutured to the lower anterior surface of the tarsus at three points. The details of the surgical procedure given in this paper are presented to illustrate the practical usefulness of a sound knowledge of the anatomy involved in ptosis."

W. S. REESE.

INNERVATION OF CILIARY BODY IN MAN. N. HIRANO, Arch. f. Ophth. **142:** 549, 1941.

The material for this study consisted of 6 human eyes (fixed in neutral solution of formaldehyde) of which frozen sections were made parallel to the outer surface of the ciliary body and stained by silver impregnation after the method of Bielschowsky and Stoehr. The motor fibers for the ciliary muscle were found to be heavy myelinated fibers which probably passed through the ciliary plexus without "making contacts" with its ganglion cells. These fibers terminated in the form of a syncytial network and not as free endings. Then there were finer nonmyelinated fibers which came from the plexus and supplied all tissue elements, favoring, however, the vascular layer and the connective tissue. These fibers Hirano calls vegetative. No sympathetic ganglion cells or afferent nerve endings were found.

P. C. KRONFELD.

Biochemistry

BIOCHEMISTRY OF THE LENS. J. G. BELLOWS and H. CHINN, Am. J. Ophth. **24:** 979 (Sept.) 1941.

These studies concern swelling of the lens. Bellows and Chinn remark the importance of water in cell life and especially "biologic water," which has such remarkable properties. They refer to the action of this water and to osmosis in the case of the lens. They give numer-

ous data obtained from experiments having to do with swelling of the lens.

W. S. REESE.

Conjunctiva

GONORRHEAL OPHTHALMIA AND GONORRHEAL OPHTHALMIA NEONATORUM. E. B. MUIR, Am. J. Ophth. **24:** 879 (Aug.) 1941.

Muir reviews the forms of treatment of gonorrheal conjunctivitis, citing various authorities. He bases the following conclusions on the records of 115 cases of gonorrheal ophthalmia and of 126 cases of gonorrheal ophthalmia neonatorum:

"Progress in the treatment of gonorrheal eye disease may be said to have made three considerable advances in the last decade. In the order of their introduction, credit for these advances must be given to: 1. Non-specific or foreign-protein therapy. 2. Artificial-fever therapy. 3. Sulfanilamide therapy. The second is closely allied to the first in its rationale. The third achieves its results in an entirely different manner and is a form of chemotherapy. In none of them is the mode of action entirely understood, and their use is fundamentally empirical. All three have reduced the length of hospitalization; all have diminished the frequency and severity of corneal complications.

"While sulfanilamide has produced more brilliant results than any previous therapeutic measure, it must be used with caution and a full understanding of its potential dangers. There will continue to be cases of gonorrheal conjunctivitis, resistant to sulfanilamide, in which recourse to all available therapeutic resources will be necessary to prevent loss of the eyes.

"The methods and procedure used by the old masters of ophthalmology must not be discarded. When properly and skillfully used, they will continue to be found of value in many cases of gonorrheal eye disease."

W. S. REESE.

PRIMARY MYCOTIC CONJUNCTIVITIS. B. V. RÉ and M. C. BLANCO, Arch. de oftal. de Buenos Aires **16:** 513 (Sept.) 1941.

A case is reported of conjunctivitis with a creamy yellowish exudate from which a fungus was isolated in Sabouraud and other mediums. This had the characteristics of Candida triadis (Langeron and Talice).

Therapeutic measures involving potassium and sodium iodide administered internally and locally proved ineffectual. A thorough final cure was obtained by intensive treatment with sulfanilamide.

A detailed description of animal experiments accompanies the paper.

C. E. FINLAY.

Congenital Anomalies

CONGENITAL MALFORMATIONS: STRANDS REPLACING BOTH SUPERIOR RECTUS MUSCLES, ABSENCE OF INFERIOR RECTUS MUSCLES, MICROCORNEA AND COLOBOMA OF IRIS; NEW OPERATIVE METHOD TO CORRECT HYPERTROPIA OF EYEBALLS; REPORT OF A CASE. M. BARTELS, Klin. Monatsbl. f. Augenh. **104:** 727 (June) 1940.

A woman aged 32 could not move her eyes upward or downward. The pupils were hidden beneath the upper lids. The condition grew

worse with advancing age, although no operation for ptosis had been performed. Bartels used a new method of operating on the two eyes, at two sittings, six days apart. After the conjunctiva was incised horizontally at the site of the insertion of the superior rectus muscle, the strand replacing it was excised as far back as possible. The conjunctiva was united in a perpendicular direction, the conjunctiva thus being lengthened. Then a horizontal incision was made through the conjunctiva over the insertion of the inferior rectus muscle, no trace of which was found, not even far back. A large crescent-shaped piece of conjunctiva was removed from the lower tip of the wound, which was closed horizontally. A double-armed guide suture was laid through the conjunctiva and the episclera at the lower limbus, through the lower fornix and through the skin, where it was fastened over a rubber tube, the eyeball thus being pulled downward. A low degree of diplopia disappeared soon after the operation, and slight motion upward and downward was noted. This effect was due to the function of the inferior oblique muscles in the author's opinion. The accompanying bilateral microcornea and coloboma of the iris are proof that macular malformations need not be of a central origin but may have a peripheral genesis.

K. L. STOLL.

Cornea and Sclera

KERATOCONJUNCTIVAL LESIONS OBSERVED AT HIGH ALTITUDES IN BOLIVIA. A. SOLARES, Am. J. Ophth. **24:** 900 (Aug.) 1941.

Solares describes a condition affecting adolescent boys, usually under 15 years of age, in the high altitudes of Bolivia. They have red eyes and contracted palpebral fissures, the redness being predominately at the limbus, either surrounding the cornea or double semilunar in configuration, the central part extending to the ends of the horizontal diameter. The color is light red, livid or violet, and in some instances the coloration is made up of fine blood vessels. There are juxtalimbal neoformations which rise above the surface of the eyeball, grayish white, with a gelatinous aspect similar to that found in vernal conjunctivitis. Solares describes this disease fully and compares it to vernal catarrh. He believes that it is a separate disease entity and designates it exuberant perikeratoconjunctivitis.

W. S. REESE.

EXPERIMENTAL KERATOPLASTY. J. A. SENÁ and M. E. JORG, Arch. de oftal. de Buenos Aires **16:** 495 (Sept.) 1941.

After a brief reference to 3 cases in which operation was performed on an opaque cornea, unsuccessful in 2 and successful in 1 (Argañaraz), 2 experimental homokeratoplasties on rabbits, with subsequent histologic examinations, are reported. In 1 experiment an extensive leukoma was first produced with the galvanocautery and the enucleation was done nineteen days after the corneal transplantation. In the other the transplantation was performed on a transparent cornea five days before the enucleation. In both a semitransparent transplant was obtained. In both the adjustment was not precise, a consequent in-dipping of the epithelium resulting, with a formation on the posterior surface of the transplant of a fibrinous deposit, where later opaque corneal tissue developed. The surrounding epithelium tended to cover the transplant,

undermining its proper epithelium. In the second experiment, in which the transplantation was made on a transparent cornea, no dividing line could be noticed between the stroma of the host and that of the transplant. In the first (in which the transplantation was performed on an opaque cornea) vascularization of the transplant was noticeable.

The authors detail histologic reactions showing the maintenance of the cellular autonomy of the transplants. The connective tissue proliferation on the posterior surface of the transplants they attribute to cellular hyperplasia of the endothelium of the host, most marked in the case in which the cornea was opaque.

C. E. FINLAY.

NEW VIEWPOINT IN ETIOLOGY OF KERATOCONUS (PRELIMINARY NOTE). A. VÁZQUEZ BARRIÈRE, Arch. de oftal. de Buenos Aires **16:** 559 (Oct.) 1941.

After an extensive review of the literature on keratoconus in its latent and in its manifest forms, with mention of the means of distinguishing the former proposed by different authors, Vázquez Barrière takes up the causation from an endocrinologic aspect, from the point of view of vitamin deficiency and from that of disturbed corneal innervation. In relation to the latter he refers especially to its production by three virus diseases: simple herpes, zona ophthalmia and venereal lymphogranuloma.

Having observed in the last-mentioned disease a greater than normal visibility of the corneal nerve filaments on slit lamp examination, a reduction of the ocular tension and a diminution of the corneal sensibility, he determined to apply the Frei test in 14 cases of keratoconus in which no symptom of lymphogranuloma except the allergic cutaneous reaction was present. In all a positive reaction was obtained.

C. E. FINLAY.

Experimental Pathology

THE ROLE OF EPINEPHRINE IN THE FORMATION OF THE INTRAOCULAR FLUID. J. S. FRIEDENWALD and W. BUSCHKE, Am. J. Ophth. **24:** 1105 (Oct.) 1941.

This study, an outgrowth of previous studies on the formation of the intraocular fluid, represents an attempt to find a humoral activator for the secretion of the ciliary processes. The following conclusions are drawn from the experiments:

"Epinephrine is a potential activator of the intraocular oxidative interaction in the ciliary body. It furnishes a link in that part of the redox chain that lies between the oxidase system of the epithelium and the interstitial mediators of the stroma."

W. S. REESE.

General Diseases

A SCOTOMA ASSOCIATED WITH MENSTRUATION. J. N. EVANS, Am. J. Ophth. **24:** 507 (May) 1941.

Evans gives the following summary of and conclusions from his investigations:

"A scotoma apparently associated with the menstrual period has been described as present in the subjects studied, and demonstrated by the technique advocated for angioscotometry. Such a defect is wedge

shaped, with its apex at the blind spot and its base located peripherally. It is one that responds to the influence of gravity, and in which transient fluctuations may be produced; as for instance by digital pressure on the eyeball. Its greatest bulk occupies the upper field, above a horizontal line 10 degrees above the fixation point. Its area and shape change with various phases of the menstrual cycle. The defect is modified by the inhalation of oxygen, and is absent during some or all stages of uncomplicated pregnancy.

"For the present, it would seem reasonable to denominate this defect, 'the scotoma of menstruation,' to assume that it is consistently present, with no more variation than one would expect of any biological process, and that it is absent during uncomplicated pregnancy. If supplementary evidence supports the findings presented here, it seems likely that angioscotometry, properly applied and interpreted, may become an extremely useful method to aid in the diagnosis of pregnancy. In this case, the scotoma of menstruation would be absent two to three days before the expected flow.

"Studies of the defect as modified by physiologic processes, disease, and therapeutic agents should be undertaken."

W. S. REESE.

EXOPHTHALMOS IN HYPERTHYROIDISM. D. KRAVITZ and W. V. MOEHLE, Am. J. Ophth. **24:** 527 (May) 1941.

Kravitz and Moehle discuss the various theories of the cause of exophthalmos in hyperthyroidism, the favorable effect of thyroidectomy in some cases and the different complications. They conclude that the exophthalmos is the result of sympathetic stimulation.

W. S. REESE.

HISTOLOGIC EYE FINDINGS IN ARACHNODACTYLY. G. D. THEOBALD, Am. J. Ophth. **24:** 1132 (Oct.) 1941.

The ocular measurements and microscopic observations in a case of arachnodactyly are reported, and the conclusion is drawn that two separate influences were responsible: First, after the fourth week an excitant caused the gigantic growth of the optic vesicle, with which the development of mesodermal tissues kept pace. Second, at the sixth month a depressant caused the arrest of development in both ectodermal and mesodermal tissues. The theories of arachnodactyly are briefly reviewed.

W. S. REESE.

General Pathology

REACTIVE FORMATION OF CONNECTIVE TISSUE AROUND CHOLESTEROL CRYSTALS IN VITREOUS OF AN ATROPHIC EYEBALL: REPORT OF CASE. VELHAGEN SR., Klin. Monatsbl. f. Augenh. **104:** 752 (June) 1940.

A woman aged 52 with high myopia had repeated intraocular hemorrhages and lost her vision in one eye owing to detachment of the retina fifteen years prior to observation by Velhagen. Finally, the somewhat phthisic eyeball became painful and had to be removed. Histologic examination revealed detachment of the ciliary body and the pars ciliaris

retinae and degeneration of the retina where it was detached at the disk. A coagulum near the disk contained remnants of blood and innumerable cholesterol crystals enclosed in a wall of collagenous connective tissue. Numerous giant cells enclosed the cholesterol crystals. A ring of fibrous tissue, measuring about 0.75 mm. in thickness, had formed around the conglomeration of crystals. K. L. STOLL.

Glaucoma

CHOICE OF OPERATION IN GLAUCOMA. O. BARKAN, Am. J. Ophth. **24:** 768 (July) 1941.

Barkan classifies glaucoma according to the location and the nature of the obstruction causing retention of intraocular fluid. He discusses the surgical procedures necessary and draws the following conclusions:

"1. Division of chronic primary glaucoma into certain types and stages according to the pathologic-anatomic classification described in this article is helpful in the management of glaucoma and in the selection of a proper operative procedure.

"2. The operation should be selected to suit the type of case and should depend on preoperative diagnosis. Ease of performance or familiarity of the surgeon with a particular operation for which he has been trained or to which he has become accustomed should be of secondary consideration.

"3. Gonioscopy with the binocular microscope is of great value in establishing the preoperative diagnosis and in arriving at the choice of operation.

"4. The incidence of permanent reduction of pressure depends upon the correct choice of operation in the individual case and the skill and experience of the individual operator." W. S. REESE.

CONJUNCTIVAL DIALYSIS. H. FERRER, Am. J. Ophth. **24:** 788 (July) 1941.

Ferrer describes an operation for those cases of glaucoma in which a filtering operation has been performed and the filtrating opening has become blocked. He makes an incision in the bulbar conjunctiva some distance from the cystoid cicatrix and then introduces a spatula to break up the adhesions. Usually these are so firm that fine-pointed scissors are necessary to snip the entire cicatricial adhesion.

W. S. REESE.

THE MECHANICAL FACTORS IN THE ETIOLOGY OF ACUTE GLAUCOMA. H. S. SUGAR, Am. J. Ophth. **24:** 851 (Aug.) 1941.

Sugar discusses the classification of glaucoma especially on the basis of gonioscopy. He suggests that the term primary glaucoma includes two distinct groups of diseases. He stresses depth of the anterior chamber, especially at the angle, as more important than congestion, and suggests an etiologic classification of glaucoma. He presents 49 case histories. W. S. REESE.

Hygiene, Sociology, Education and History

AN OCULAR POLICY FOR PUBLIC SCHOOLS. R. IRVINE, Am. J. Ophth. **24:** 799 (July) 1941.

This comprehensive committee report on the examination of children's eyes in public schools and on problems pertaining thereto is taken up under the headings: (1) methods of examination, (2) preventive measures, (3) reading problems and (4) care of patients unable to pay a private physician.

W. S. REESE.

Lens

REMOVAL OF THE LENS IN HIGH MYOPIA IN WHICH LENTICULAR OPACITIES PREVENT IMPROVEMENT OF VISION BY CORRECTING LENSES. B. CHANCE, Am. J. Ophth. **24:** 519 (May) 1941.

Chance reports 6 cases of high myopia in which the lens was removed satisfactorily. He concludes that the myopic eye can withstand the incision and manipulation incident to modern methods of cataract extraction.

W. S. REESE.

CHOLESTEROL CRYSTALS IN THE NUCLEUS IN CORONARY CATARACT. E. PURTSCHER, Arch. f. Ophth. **142:** 588, 1941.

By microscopic examination in polarized light and by a microchemical test the author could show in an intracapsularly extracted lens that the well known, and fairly common, apparently needle-shaped crystals in the nucleus of cataractous lenses actually consist of platelets of cholesterol.

P. C. KRONFELD.

DENSE OPACITY OF VITREOUS OBSERVED AFTER INTRACAPSULAR EXTRACTION OF CATARACT. H. FANTA, Klin. Monatsbl. f. Augenh. **105:** 241 (July) 1940.

A woman aged 78 had beginning senile cataract and opacities in the vitreous of the right eye, with vision of 3/36, and nuclear cataract, with vision reduced to perception of hand movements, in the left eye. Light projection was normal. No indication of previous ocular inflammation was found in examination with the slit lamp. The cataract in the left eye was uneventfully extracted by the intracapsular method. After delivery of the lens, it was noticed that the pupil was not black but grayish white. Examination showed the presence of a hernia of the densely opaque vitreous. The eye recovered, but the fundus remained cloudy and vision was limited to perception of hand movements.

K. L. STOLL.

Neurology

PRESERVATION OF CONVERGENCE WITH PARALYSIS OF ALL LATERAL MOVEMENTS IN A CASE OF INTRAMEDULLARY TUMOR OF THE PONS. W. S. REESE and J. C. YASKIN, Am. J. Ophth. **24:** 544 (May) 1941.

Reese and Yaskin report the case of a 47 year old woman who could move her eyes up and down in convergence but could not move

them from side to side. A diagnosis of tumor of the pons was made and confirmed at operation. A number of similar cases are cited and commented on. It is concluded that such ocular findings are of localizing value, indicating a tumor of the pons. W. S. REESE.

CHOKED DISCS IN LEAD ENCEPHALOPATHY. P. GOOD, Am. J. Ophth. **24:** 794 (July) 1941.

Good reports 2 cases of lead poisoning in children, in 1 of which it was complicated by brain tumor. He gives the following summary:

"1. Lead poisoning must be considered in children who show signs of increased intracranial pressure and choked discs.

"2. Roentgenographic density in the growth line of the long bones is a valuable aid in the diagnosis of lead poisoning.

"3. Drs. Buchanan and Bucey have shown in several cases that the severity of complications and the mortality of lead encephalopathy can be reduced by a decompression in addition to the approved medical treatment." W. S. REESE.

Ocular Muscles

CONVERGENCE INSUFFICIENCY. B. CUSHMAN and C. BURRI, Am. J. Ophth. **24:** 1044 (Sept.) 1941.

Cushman and Burri arrive at the following conclusions:

"1. Adduction and finger-convergence exercises were given to patients who after a cycloplegic refraction and proper fitting of glasses, had (a) an exophoria that was greater for near than distance; or (b) who had an exophoria for near only, and in conjunction with it, or alone, adduction weakness or generally poor abducation and adduction balance and subjective symptoms; or (c) who had no exophoria but only poor abduction and adduction balance.

"2. Training was continued until normal ductional reserve was established and until the symptoms disappeared.

"3. The exophoria is not necessarily eliminated by the exercises, but duction reserve was developed in order that the patient might cope with the existing phoria.

"4. At times the symptoms were complicated by psychologic or neurotic manifestations. In those cases attempt was made to aid the patient in solving his personal problems. This reacted favorably upon the progress of the training.

"5. If other complications existed medical care was advised. In several cases glandular disturbance was found and controlled, also a few cases of mild vitamin-B deficiency. Both conditions materially affected the muscle balance.

"6. In children with reading difficulty a complete psychologic examination was made and specific reading aid advised in addition to the ocular exercises.

"7. Fifty-three of the 80 patients recovered completely from their symptoms, and of those whom we had the opportunity to recheck after various intervals, almost all remained without symptoms and their ductions have stayed within normal limits." W. S. REESE.

ATYPICAL OCULAR TORTICOLLIS CAUSED BY ABSENCE OF INFERIOR RECTUS MUSCLE. P. A. JAENSCH, Klin. Monatsbl. f. Augenh. **104:** 733 (June) 1940.

Ocular torticollis is usually caused by paralysis of the trochlear muscle. Jaensch reports on a boy aged 13 with forced inclination of the head to the right side caused by complete absence of the right inferior rectus muscle, coupled with excess function of the right superior rectus muscle. The concomitant action of the retina of the two eyes was abolished. Alternating strabismus sursum vergens existed. The condition appeared to be a congenital malformation consisting of absence of the right inferior rectus muscle. The torticollis was eliminated by recession of the superior rectus and advancement of the inferior rectus muscle together with its fascia and a coarse strand. The evidence of cases of this type is opposed to the theory that strabismus is due to disturbed fusion.

K. L. STOLL.

Orbit, Eyeball and Accessory Sinuses

ORBITAL TUMORS AND THEIR SURGICAL TREATMENT. A. B. REESE, Am. J. Ophth. **24:** 497 (May) 1941.

This is the second part of an article on orbital tumors and deals with nasopharyngeal lesions and lesions of the sinuses, eyes and lids, these being the causal factor in 90 per cent of cases of exophthalmos caused by lesions adjacent to the orbit. The diagnostic value of roentgen examination and biopsy (aspiration and surgical) is emphasized, and different surgical indications mentioned.

W. S. REESE.

OCULAR HYPERTELORISM OF GREIG. E. A. VORISEK, Am. J. Ophth. **24:** 928 (Aug.) 1941.

Vorisek defines hypertelorism as abnormally widely separated eyes said to be the result of maldevelopment of the sphenoid bone. He enumerates its characteristics and reports 4 cases, in 3 of which photographs or roentgenographs or both proved the diagnosis.

W. S. REESE.

HYPEROSTOSIS OF THE ORBIT. W. L. BENEDICT, Am. J. Ophth. **24:** 1005 (Sept.) 1941.

Benedict discusses bony tumors of the orbit and their diagnosis. He divides them into (1) osteomas, or tumors arising from the nasal sinuses and extending into the orbit, and (2) exostoses and hyperostoses, or tumors arising from the surface of a bone as nodules, projections or diffuse thickening and hypertrophy of the bone in response to irritation from contiguous pathologic processes. He discusses these tumors and reports 12 cases.

He concludes that such tumors should be removed through the orbit or transcranially according to the facts in each case.

W. S. REESE.

Parasites

OCULAR ONCHOCERCIASIS. A. QUEVEDO, Am. J. Ophth. **24:** 1185 (Oct.) 1941.

Quevedo describes generalized and ocular onchocerciasis, and gives the following summary:

"American onchocerciasis should be considered as an ocular affection. Only complications in the eyes are serious.

"The nodules ought to be excised. When cases of onchocerciasis present themselves without apparent tumors, these should be searched for with great care.

"Treatment to destroy the microfilaria will avert ocular complication. Such treatment is still to be discovered."

W. S. REESE.

Refraction and Accommodation

TRANSITORY MYOPIA. S. S. BLANKSTEIN, Am. J. Ophth. **24:** 895 (Aug.) 1941.

Blankenstein gives the following summary:

"1. Transitory myopia occurs largely from the local ocular disturbances such as trauma and iritis and from general systemic diseases such as diabetes.

"2. Drug therapy is an important etiological factor in its production, especially from arsphenamine preparations and sulfanilamide.

"3. The importance of sulfanilamide is attested by the fact that it is now in general use. The method by which it causes myopia is not entirely known. The case here reported would rule out ciliary spasm as a factor and would lead to the conclusion that it is more likely a reaction on the part of the lens either on an allergy basis or as due to a difference in the osmotic tension of the lens as compared to the aqueous produced by the unequal distribution of sulfanilamide within the eye."

W. S. REESE.

Retina and Optic Nerve

RETINAL TELETRAUMATISM. J. W. SMITH, Am. J. Ophth. **24:** 537 (May) 1941.

Smith reports the case of a 46 year old man whose machine was struck head on by a truck. When he was first seen, there was pronounced ecchymosis of the lids, and the pupils were dilated and did not react. The right disk appeared white, and there were many small retinal hemorrhages. The left disk appeared pale, but there were no hemorrhages. A diagnosis of Purtscher's disease was made in the case of the right eye, and follow-up notes on the changes that occurred in both eyes are given. The literature is briefly reviewed and the term teletraumatism suggested rather than Purtscher's disease in order to bring such cases into one general group.

W. S. REESE.

RETINAL TUBEROUS SCLEROSIS (BOURNEVILLE'S DISEASE). A. LOEWENSTEIN and J. STEEL, Am. J. Ophth. **24:** 731 (July) 1941.

Loewenstein and Steel give the following summary:

"The case described was observed in a boy of 3½ years, with no history of hereditary defect. He had epileptic fits, but presented no sebaceous adenomata. Ophthalmoscopic examination showed gray-green tumors, exudative retinitis, retinitis proliferans, and angiomatous nodules. Upon subsequent examination, the picture changed. Anatomical examination of the other eye showed multiple tumors with nerve fibers and regular layers straight as an arrow—neural cells producing closed and open cysts, a thickened membrana limitans interna, pyramidal tumor of the disc, and lack of the bacillary layer. Also present was a typical choroidal angioma and angiomatous growth at the retinal surface.

"We assume that the round nucleated tumor cells arise from the round cells of the inner wall of the optic cup which normally would have developed into ganglion cells—they grow in single layers and produce cysts. A mechanical explanation of the genesis of cysts is given.

"The condition is a *primary ectodermal* malformation and the disturbance of balance of ectoderm and mesoderm leads *secondarily* to a *mesoderm* tumor. The opposite sequence occurs in Hippel-Lindau's disease, the *primary* growth being *mesodermal* and the *secondary ectodermal.*

"All four of the phacomatoses arise from congenital, usually hereditary malformations, in which certain undifferentiated cells start to grow and bring disorder into the germinal layers by disturbing the mutual pressure of the tissue (Gurvič) needed for a normal development. The drive of growth is assumed to be a chemical one—parallel to the carcinogenic substances, a surplus of which produces a growing tumor. A defect causes the different kinds of regressive metamorphoses known as familial degenerations of cerebrum, retina, cornea, and other tissues."

W. S. REESE.

DETACHMENT OF RETINA CAUSED BY RUBBING EYE: REPORT OF CASE. K. LINDNER, Klin. Monatsbl. f. Augenh. **105:** 118 (July) 1940.

An inquiry by an oculist whether detachment of the retina might have been caused by rubbing of the eye after a lime solution got into it was answered in the affirmative by Löhlein. He was uncertain, however, whether or not the process of cleansing the eye, including eversion of the lid and irrigation, might have been responsible for the retinal detachment. Lindner arrived at the same opinion. He contends that rents in the retina may be caused by degeneration and that a degenerated retina may tear in consequence of rubbing of the eye. Incidentally, Lindner refers to a case reported by Vogt, in which a forceful turn of the eye upward caused retinal detachment. Examination of the vitreous is essential. The detachment of the retina must be considered as an ordinary pathologic occurrence if the vitreous is detached.

K. L. STOLL.

Tumors

GLIOMAS OF THE RETINA. E. M. PARKHILL and W. L. BENEDICT, Am. J. Ophth. **24:** 1354 (Dec.) 1941.

Parkhill and Benedict conclude as follows:

"A series of 35 tumors of the retina was studied and, on a histologic basis of differentiation of tumor cells, was divided into two groups, an extremely undifferentiated retinoblastoma type, and a partially differentiated neuro-epithelioma type. A third, well differentiated astrocytoma type, an example of which was reported by McLean, was not represented in this series. The following conclusions were drawn:

"1. Neuro-epitheliomas seldom, probably never, arise from the rod-and-cone cells of the retina.

"2. Gliomas of the retina of any type arise most often in the inner-nuclear layer, less frequently in the ganglion-cell and nerve-fiber layers, and rarely, if ever, in the outer-nuclear layer.

"3. In cases in which regions of normal retina still persist, an appearance of multicentric origin of tumors is frequent.

"4. Retinal tumors probably do not arise from embryonic rests nor from persistent primitive epithelium, but from normal cells that have dedifferentiated to produce tumor cells.

"5. The cells from which the tumors arise are probably most frequently, if not always, glial cells.

"6. The most undifferentiated of the tumor cells are the small cells with hyperchromatic polygonal or wedge-shaped nuclei that predominate in the retinoblastomas; they are extremely anaplastic and do not correspond necessarily to any known cell of normal retinal embryogenesis.

"7. Cells in rosettes are not rod-and-cone cells and are much less differentiated than are rod-and-cone cells.

"8. The formation of rosettes is an evidence of partial differentiation of the tumor cells to a point at which they resemble more or less closely the cells of the primitive neural tube.

"9. The formation of pseudorosettes also signifies differentiation of the tumor cells, probably almost to the degree attained by the cells of true rosettes. The alignment of epithelial-like cells into rows and bands, sometimes surrounding blood vessels, also is a manifestation of a slight degree of differentiation.

"10. Results in the retinoblastoma group were poor (only two cases with good results, or 12.5 per cent of 16 traced cases), as compared with those in the neuro-epithelioma group (10 cases with good results, or 62.5 per cent of 16 cases traced)."

W. S. REESE.

DIKTYOMA OF THE CILIARY BODY. I. CZUKRÁSZ, Arch. f. Ophth. **142:** 619, 1941.

The blind left eye of a boy 3 years of age was removed because of inflammation and a yellow reflex from the fundus suggesting glioma. Histologic examination revealed a diktyoma (Fuchs), a neoplasm arising from the unpigmented epithelium of the ciliary body and resembling

embryonic retina. The author considers the tumor to be benign, which is contrary to the opinion of Fuchs and others. An incomplete review of the literature is given.

P. C. KRONFELD.

Uvea

BOECK'S SARCOID WITH NODULAR IRITIS IN A CHILD. P. S. THORNHILL and E. H. THORNHILL, Am. J. Dis. Child. **64**: 262 (Aug.) 1942.

Because of the rarity of ocular lesions of Boeck's sarcoid in children, the Thornhills report the case of a Negro girl of 9. The differential diagnosis comprised tuberculous iritis, syphilitic iritis and Boeck's sarcoid. By physical and roentgenographic examination, intradermal tuberculin and Wassermann tests, repeated examinations of the sputum, inoculations of guinea pigs and microscopic study of a lymph node, the diagnosis of Boeck's sarcoid was established. The course of the sarcoid is protracted, with a decided tendency toward healing. The disease is rarely fatal. The patient was given a high calory, high vitamin diet containing cod liver oil, ascorbic acid, thiamine hydrochloride and brewer's yeast. One drop of 0.5 per cent atropine sulfate solution was used in the affected eye three times a day. During her stay in the hospital (four weeks) she had a temperature of 98.5 and 100.4 F. but seemed to feel fine, ate well and gained 1½ pounds (680 Gm.). The condition of the eye remained essentially the same; there was no improvement at discharge. One month later the vision in the affected eye (20/400) was unimproved. The corneal haze and the descemetitis had cleared somewhat. Vascularization on the posterior surface of the cornea was seen. The pupil was poorly dilated, owing to posterior synechias. Large cystic nodules on the iris had cleared. In the iris on the nasal side were four compact pinhead-sized yellow granules. Pigmented deposits were still present on the anterior surface of the lens. The posterior segment could not be visualized. Roentgen study of the chest showed considerable regression of the enlargement of the lymph nodes, but the peripheral lung fields probably showed slightly more mottling than on previous examination. Roentgenograms of the hands, feet and long bones still revealed no cystic changes.

J. A. M. A. (W. ZENTMAYER).

Society Transactions

EDITED BY DR. W. L. BENEDICT

COLLEGE OF PHYSICIANS OF PHILADELPHIA, SECTION ON OPHTHALMOLOGY

ALFRED COWAN, M.D., *Chairman*

WARREN S. REESE, M.D., *Secretary*

October 15, 1942

Posterior Phlyctenular Keratitis. DR. G. G. GIBSON.

The case was reported of a white woman aged 36 who had had recurrent episodes of ocular inflammation since childhood and was found to have active and healed phlyctenules and phlyctenular pannus on the anterior surface of the cornea. While she was under treatment there developed on the posterior surface of the cornea a slowly progressive lesion, which eventually extended well into the pupillary area and seemed destined to involve the entire cornea. It was characterized by a dense yellowish crystalline deposit which was vascularized. The adjacent part of the cornea was normal. This deposit was interpreted as an allergic posterior phlyctenule which spread by its own presence in contact with normal cornea.

Five delimiting keratotomies were performed in an effort to prevent further extension. They were rather successful in stopping spread of the main lesion, although the cornea became somewhat infiltrated beyond the surgical scar. The degree and the frequency of appearance of the ocular inflammation were materially benefited by an extensive course of old tuberculin therapy extending over a three year period.

DISCUSSION

DR. G. P. MEYER: It is difficult to discuss a subject one has never heard of before. A phlyctenule ordinarily is looked on as a cellular response to an allergic hypersensitivity in a certain site. In phlyctenular keratitis the allergic, or sensitized, site is in the cornea, and with the introduction into that site of the reacting agent, a cellular response appears. That response, as a matter of fact, is a small pustule.

One cannot question the diagnosis of the essayist with regard to the initial episode in his case, because it consisted in the appearance of a true phlyctenule. But the second episode, in which the major response was a crystalline deposit, leaves one a little confused.

Crystalline changes in the eye are, of course, not new. They occur in the cornea as degenerative changes with accompanying scar tissue. They have been found in the anterior chamber simulating hypopyons and are found in rare occasions on the iris. These changes usually are degenerative and not inflammatory or allergic.

It would be rather hard to explain why the response in the cornea in this particular case was crystalline in character. It might be that

there was some local disturbance in the oxidation processes in the cells; there might have been some degenerative process initiated by the adjacent inflammatory process. But there is the possibility of the diagnosis of a dual lesion, an initial classic phlyctenular keratitis followed by some disturbance marked by crystalline deposits as a secondary manifestation.

Regarding the treatment, delimiting keratotomy used to confuse me because it was hard for me to understand the value of cutting off the blood supply to a lesion that one hoped to heal. But I have learned that the purpose of this operative procedure is not to cut off the ingress of immunologic or healing agents, but rather to restrict exciting agents from approach to the wound. Delimiting keratotomy, too, confused me because I could not understand why it had any therapeutic value other than the induction of hypotony and the introduction into the eye of new fluids with a higher content of immune bodies. But I have since read that this procedure has an additional value in the epithelization of the wound, because the epithelial ingrowth in the superficial layers of the cornea acts as a barrier.

The most interesting therapeutic agent in the case reported is the tuberculin. Clinically, it is well known that because of the etiologic relation of tuberculosis to phlyctenular keratitis desensitization with tuberculin is a valuable procedure.

One point that might help in establishing whether the second crystalline condition was truly a manifestation of hypersensitivity to tuberculin or to the phlyctenular state would be the effect of the tuberculin on the lesion. Dr. Gibson stated in his paper that when the tuberculin therapy was stopped, symptoms recurred. I should like to know whether there was any corneal response to the cessation of this treatment; whether the deep lesion improved and grew worse with the giving and the not giving of the tuberculin.

Knowledge of such a response would be a valuable help in establishing the tuberculous nature of the deep lesion. When Dr. Gibson said that the lesion grew worse I wondered what the character of the response was, because if there was a new access of activity of the deep lesion, I would take it to mean that the crystalline deposit was truly a phlyctenular manifestation.

DR. H. M. LANGDON: If I understand Dr. Meyer correctly, he is doubtful as to the justification of the diagnosis of posterior phlyctenular keratitis. It seems to me that Dr. Meyer's doubt is justified. To him, a phlyctenule is a definite entity and has a definite location. It seems to me that a somewhat better diagnosis would have been interstitial keratitis of tuberculous origin.

DR. W. ZENTMAYER: Some years ago Dr. W. G. M. Byers, of Montreal, discussed a lesion which appeared in conjunction with a superficial phlyctenule and resembled somewhat the condition described by Dr. Gibson. With the slit lamp one could see a white opacity in the deeper layers of the cornea anterior to Descemet's membrane. But it was concurrent with the primary phlyctenule on the cornea.

DR. ALFRED COWAN: In my opinion Dr. Gibson was justified in diagnosing the condition as phlyctenular keratitis. Phlyctenular keratitis frequently starts deep. As a matter of fact, it always starts in the

substantia propria, even though it is seen first in the bulbar conjunctiva. The epithelium is always affected later, and the ulcer is formed when necrosis of the overlying epithelium develops. The first appearance of phlyctenular keratitis is in the anterior portion of the substantia propria beneath Bowman's membrane.

Often if one looks with the corneal microscope and slit lamp, one sees deep infiltration in phlyctenular keratitis. In most cases, when it starts deep one even observes deep vascularization: vessels coming from the ciliary system. They do not always come over superficially.

If a healed ulcer after phlyctenular keratitis is examined with a narrow beam of the slit lamp carefully, one sees that the scar is always considerably below the level of the new-formed epithelium. Healing of the epithelium probably took place before the lesion itself was healed. Often there is a perfectly regular and smooth anterior surface, although it looks on ordinary examination very much like a depressed scar.

DR. G. G. GIBSON: I wish to thank the discussers for their enthusiastic participation. It proves my original statement that this case illustrates some controversial points in corneal disease.

First, Dr. Meyer brought up some questions which are difficult to answer and which are much to the point. I am quite in agreement with Dr. Meyer's explanation of this case. The lesion represented an allergic manifestation of tuberculous disease.

Persons who would demand the isolation of organisms or positive histologic evidence of tuberculosis would be disappointed; there was no evidence of tuberculosis as such. The diagnosis had to be made on clinical bases. It was unfortunate that there were no roentgenograms and no specimens of sputum providing positive evidence; one had to be content with a diagnosis based on less conclusive evidence. Nevertheless, a diagnosis was necessary, and my point about the allergic nature of the condition was, I believe, unquestionably true. Why the lesion should have been fundamentally a crystalline lesion is difficult to answer, but I feel it was because there was a low grade allergic inflammatory process deep in the cornea, which differed from the superficial variety of phlyctenular keratitis in that there was no drainage mechanism. The superficial variety of phlyctenular keratitis can ulcerate and drain, but this lesion, deep in the substantia propria, could not drain, and it differed from ordinary corneal disease in that it extended, not because of the extension of infection, but because of its presence—its own presence—in the cornea.

In other words, the lesion made pressure on the adjacent normal portion of the cornea and that became involved, so that the metabolism of that part of the cornea was interfered with, a fatty degeneration and crystalline deposit in the cornea being produced. As I watched the lesion with a slit lamp, this mechanism could be determined to be at work. The margin of the lesion was absolutely free from edema and free from infiltration. There was no evidence of keratitis other than the phlyctenular type.

Dr. Meyer asked why keratotomy worked. It is difficult to say, but it probably worked because scar tissue was formed in the incision and when the lesion came in contact with the film of scar tissue it no

longer came in apposition with the normal cornea. Then it could not cause the pressure against the normal cornea which allowed it to extend.

In answer to Dr. Meyer's question about the effect of old tuberculin, I must confess that I do not have the evidence he demanded, in that there was no improvement in the lesion, as far as the lesion per se was concerned, with the use of old tuberculin. The appearance did not change when the patient stated that the eye felt better or that it felt worse, but there was a change in the vascular reaction. The ciliary injection and the photophobia were diminished at the time she stated that the eye felt better, but the appearance of the lesion did not change.

I think that these circumstances fit in with the fact that the purpose of the old tuberculin was not to modify the course of the lesion but to produce a desensitization of the patient to the tuberculous protein; I therefore think they are consistent with the nature of the lesion and explain why there was no change in the appearance of the lesion when it did improve subjectively.

Dr. Langdon's objection really did not apply in this case, because it is not a case of tuberculous keratitis. There was none of the infiltration and edema or any of the features which go with interstitial keratitis. It is because of the fact that the condition in my case was so different in all respects from the condition Dr. Langdon mentioned that I considered it worthy of reporting. Keratotomy could be contraindicated in tuberculous interstitial keratitis.

Etiologic Role of Focal Infection in Diseases of Eye. DR. M. SOLIS-COHEN.

The etiologic role of focal infection in diseases of the eye has been recognized for at least three hundred years, having been referred to by Riverius, Fernelius and Steno, writing in the seventeenth century. Among the many distinguished ophthalmologists who have stressed the relation between focal infection and certain diseases of the eye are Brunton, Bryan, de Schweinitz, Mackenty, Lang, MacKenzie, McConachie, Knapp, Posey, Risley, Shumway and Zentmayer.

The presence of tuberculosis or syphilis does not rule out focal infection as the cause of an ocular condition. Among the diseases of the eye of which focal infection has been demonstrated to be one of the etiologic factors are conjunctivitis, scleritis, episcleritis, uveitis, choroiditis, keratitis, iritis, retinitis, optic neuritis, retrobulbar neuritis, amblyopia, amaurosis, ptosis, strabismus and paralysis of the muscles of accommodation. Ocular symptoms of bacterial toxemia from focal infection are burning of the eyes, blurring of vision, scotomas, asthenopia, ocular fatigue (especially after a slight amount of near work), impairment of accommodation and weakness of convergence.

Focal infection may exert a baneful influence on eyes that have been operated on, keeping up the inflammation and being responsible for secondary infection.

The conception of foci of infection should stress infecting organisms rather than infected tissue. When bodily resistance is weakened by fatigue, trauma and other factors, the infecting bacteria in the primary focus metastasize and produce a focal infection. The trauma of an operation on a focus of infection, by lowering bodily resistance, may

spread the infection to the heart, kidneys, joints and eyes. The danger may be minimized by exercise of gentleness, avoidance of multiple tooth extraction and raising of resistance by preoperative and postoperative care, preoperative autogenous vaccinotherapy and administration of a sulfonamide compound preoperatively and postoperatively.

To influence the focal infection favorably, the operation must be performed on the etiologic, or primary, focus; secondary foci should not be neglected, and all infected tissue should be removed. The surgeon's knife, however, does not remove the infecting microbes, which remain until overcome by the patient's defensive forces. Such forces may occur spontaneously but frequently require artificial stimulation of production of antibodies by the administration of a potent autogenous vaccine, preferably a pathogen-selective vaccine.

DISCUSSION

DR. H. M. LANGDON: Dr. Solis-Cohen's paper is all embracing, but I fear it was read before the wrong section. My difficulty is in getting laryngologists to take active steps in cases in which there is a probable focus of infection, especially in the sinuses, unless they find some acute, flagrant condition.

In my experience it has been low grade hyperplasia of the lining membrane of the sinuses which has produced ocular conditions. I do not remember ever having seen an ocular infection from an acute, flagrant outburst of sinus infection. The cases which have baffled me are the ones in which the laryngologist was apt to say, "There is no sinusitis at all," and yet I had excluded other etiologic factors by dental roentgenograms, general examination, etc.

One case I remember particularly was that of a woman who had uveitis. Dr. Ross Skillern saw her and operated on the sphenoid on the affected side, and the eye cleared up promptly. Dr. Skillern died, and within two years after his death the patient's other eye became similarly involved. She went to another excellent rhinologist, who assured me that there was nothing in the sinuses that could possibly cause the trouble. The patient's vision deteriorated to 5/60, and I asked the rhinologist if he would please do something because I knew the cause was the sinus condition. The rhinologist did operate for a low grade sphenoiditis, which he had been treating, and immediately the eye began to clear up. The woman had 5/4 vision on the side which was promptly operated on, but on the other side the vision never improved beyond 5/10, because the damage was done. Had the rhinologist acted more promptly, I am sure that there would have been as good a result on this side. I have had this sort of experience often. Rhinologists seem averse to taking active steps unless there is a flagrant, outspoken set of symptoms to guide them.

From my experience, dentists are quick to cooperate. They are guided by their roentgenograms and act accordingly. I should like to ask Dr. Solis-Cohen one thing: Did he find any reference among the cases of dental infection to what is now called an apical abscess of a tooth? Or was the condition simply referred to as a tooth infection or a mouth infection? I have often wondered exactly how far back the apical abscess was recognized as a definite entity.

DR. M. SOLIS-COHEN: I am sure that Dr. Langdon knows all about focal infection, having been an assistant of de Schweinitz, but he

probably does not realize that most of the recent books on ophthalmology ignore focal infection.

The older writers did not speak of apical abscesses. The teeth pulled out a hundred years ago were, as a rule, badly infected teeth. It may be that in some cases they regarded teeth with apical abscesses as normal. Before the advent of the theory of focal infection, the action of the diseased tooth was thought to be a reflex one. The ophthalmologist diagnosed iritis and pulled the tooth out, and the patient got well. Possibly some cases I cited as instances of focal infection were really cases of a lesion reflex in nature.

I have had a quarrel with the laryngologists for twenty-five years. I have read papers before the otolaryngologic section of this college and before the Philadelphia Laryngological Society, and I still feel that the laryngologists do not understand the nature of focal infection or of foci of infection. When a laryngologist has taken out a pair of tonsils, he says that he has removed the focus of infection and tells the referring physician that there is no longer any focal infection. If a patient came with the tonsils out, he would look into the throat and say that there was no focus of infection present. Yet the infecting organism that had originally been present in the tonsils would now be in the tonsillar fossae, or on the tonsillar pillars and adjacent tissues, and in the nasopharynx, where it would continue to infect the patient. In other words, the focus of infection would remain. There would be no diseased tissue present, however, and without such tissue the otolaryngologist would not recognize an infection.

Skillern nineteen years ago, in discussing my paper on "The Rhinopharynx as a Site of Focal Infection," said that unless he could see diseased tissue in the rhinopharynx he would not believe that infection existed there (Skillern, R. H.: Discussion on the Rhinopharynx as a Site of Focal Infection, *Tr. Coll. Physicians, Philadelphia* **45:** 655, 1923).

Otorhinolaryngologists have the same attitude toward sinusitis. Unless they see pus coming out of a sinus they say that the sinus is normal, which often is not the case. After they have opened and drained the sinus they say the focus of infection has been removed, and yet the infecting organisms are still in the sinus and in the nares. Draining a sinus does not make these bacteria vanish. One cannot force an otorhinolaryngologist to open a sinus that looks all right to him. Therefore, when convinced that the sinus is a focus of infection, I make a vaccine to increase the patient's resistance—his production of antibodies—so that the newly formed antibodies in his blood, whose production is thus stimulated, will cure the infection the otorhinolaryngologist will not treat.

A Classification for Congenital Ptosis. DR. E. B. SPAETH.

A series of cases of congenital ptosis was analyzed and classified according to unilaterality and bilaterality and the presence of an accompanying paralysis of the superior rectus muscles, unilateral (homolateral or contralateral) or bilateral; of paralysis of the contralateral third, fourth or sixth nerve; of other congenital defects of the lids and the palpebral fissures; of the jaw-winking reflex, and of a retraction syndrome. As a result of this analysis, eight general classes appeared, as follows: class 1, unilateral ptosis without any other defects, 40 per cent

of all cases; class 2, unilateral ptosis with involvement of the homolateral superior rectus muscle, 21 per cent of all cases; class 3, bilateral ptosis without involvement of the superior rectus muscles, 7 per cent of all cases; class 4, bilateral ptosis with involvement of the superior rectus muscles, 8 per cent of all cases; class 5, unilateral ptosis with involvement of both superior rectus muscles, frequently more pronounced in the homolateral eye, 1 per cent of all cases; class 6, ptosis with more or less complete paralysis of the third and even of the fourth and sixth nerves, 9 per cent of all cases; class 7, ptosis with the classic jaw-winking reflex, 2 per cent of all cases, and class 8, ptosis with the Duane's retraction syndrome, 2 + per cent of all cases.

The surgical treatment of these conditions was then considered on the basis of the anatomic findings present in any one class, to emphasize the truth of the statement made that one operation would fit only one type of case or group of anatomic conditions. Varied surgical measures are a definite necessity for the proper correction of these conditions. The other extraocular defects present in any one case must be corrected before the drooping lid itself can be operated on. Early diagnosis and adequate surgical care depending on the surgical therapy indicated are needed, and the operator must not fit an operation which he prefers to do to all cases.

DISCUSSION

DR. W. I. LILLIE: I enjoyed Dr. Spaeth's presentation. He brought out very well that even with the many classifications of ptosis one has available three general types of surgical procedures for correcting congenital ptosis.

The interesting clinical aspect of ptosis is to try to correlate at as early an age as possible the probable cause. The ptosis may be due to an organic central lesion, intramedullary midbrain, extramedullary or oribital. If not, as the child grows the ptosis may improve. I agree with Dr. Spaeth that one should not hastily institute a surgical procedure in too young a patient.

If organic lesions are eliminated in the differential diagnosis, the choice of surgical procedure depends on the clinical findings. If there is no action of the levator, for one to utilize that muscle, expecting to get lid action, would be faulty judgment. The superior rectus muscle is also usually affected, either partially or completely, and operations directed toward use of the levator or of the superior rectus muscle produce end results that are not always gratifying to the patient, to the parents or to the surgeon. One frequently has to resort to using a muscle, the fronto-occipital, which is not meant to have any direct function in lifting the lid. As a matter of fact, the normal action of the lid is not a lift. The action of the levator pulls the upper lid back over the eyeball; so a normally placed eyeball is also necessary for proper function.

Fortunately from the clinical standpoint, use of the fronto-occipital muscle usually produces a cosmetic improvement. The numerous types of surgical procedures involving utilization of the frontalis muscle reveal that something is wanting from the surgical and cosmetic points of view in any one or even in combinations of these procedures; but in cases of severe involvement, even though a perfect function of the lid is not obtained, the improvement is sufficient to warrant surgical inter-

vention. The patient and the relatives should be told without hesitation that a perfectly normal lid action is not to be expected. So, all in all, the surgical treatment of congenital ptosis still leaves much to be desired both anatomically and cosmetically.

DR. E. B. SPAETH: I wish to thank Dr. Lillie for his discussion. There is just one more word I want to say: The importance of the whole affair is that in 35 per cent of cases of ptosis the situation is complicated; that is, there are factors of importance beyond the simple drooping of the lid and the epicanthus. These are the cases Dr. Lillie was referring to in which varied surgical procedures are necessary.

A cosmetic result that one knows is a wretched physiologic operation may satisfy the patient's parents. On the other hand, I have been pleased with results which I thought were good physiologic successes and have had the patient's parents say, "Well, the eyelid isn't much better, is it?"

Book Reviews

War Medicine: A Symposium. Edited by Winfield Scott Pugh and others. Price, $7.50. Pp. 565. New York: New York Philosophical Library, Inc., 1942.

This book is the result of the joint efforts of many authors, each of whom has contributed a chapter on some special phase of military medicine. It covers a wide range of subjects, which are classified under the headings of surgery, aviation, naval medicine and general medicine. The chapters of particular interest to the ophthalmologist are "Ocular and Orbital Wounds in War," by William B. Doherty; "Ophthalmic Casualties Resulting from Air Raids," by Dorothy R. Campbell, and "Shamming Night Blindness," by N. Bishop Harmon.

In his discussion of ocular and orbital wounds, Dr. Doherty first reviews the anatomy of the orbit and then points out the types of lesions produced by different kinds of injuries. In his analysis he quotes freely from his own experiences and from the writings of Lagrange. Particular emphasis is placed on the necessity of a thorough examination in any case of injury of the eye and orbit, and a comprehensive outline of the procedures to be employed is given. The following five unusual conditions found in war are discussed: traumatic proliferating choroidoretinitis of Lagrange, (2) spastic entropion (blepharospasm), (3) avulsion of the optic nerve, (4) enophthalmos (true and false) and (5) hematic pigment ring of the disk. For the correction of spastic entropion Dr. Doherty describes his operative technic, which consists of (1) excision of a crescentic strip of orbicularis muscle from the entire length of the lower lid and (2) closure of the wound. The sutures are placed in the skin of the upper part of the incision and then in a horizontal direction in the tarso-orbital fascia before being brought through the lower edge of the cutaneous incision. Intraocular foreign bodies are briefly discussed by means of a few case reports.

Ophthalmic casualties resulting from air raids appear to be due to (1) explosive incendiary bombs, (2) the sudden compression and expansion of the atmosphere caused by blast and (3) direct blows on the eye. Incendiary bombs often cause multiple foreign bodies to be embedded in the eyelids, conjunctiva and cornea. Dr. Campbell wisely cautions against attempting to remove all of the foreign bodies at one time. Softening of the ocular tissues was most striking, so that, in her experience, primary suturing was frequently unsuccessful.

The injuries produced by blast were (*a*) proptosis due to retrobulbar hemorrhage with immediate loss of vision, (*b*) extensive intraocular hemorrhage either from an iridodialysis or from rupture of a retinal vessel, (*c*) rupture of the choroid and (*d*) acute iritis and acute secondary glaucoma. The recording of experiences with these injuries constitutes a valuable contribution to our knowledge of ophthalmic injuries.

In the brief article on shamming night blindness, a test is described by which Dr. Harmon has been successful in detecting malingering. The test is as follows: Two Snellen test types are fixed one on each

surface of the same board. On one side the regular range from 6/60 to 6/6 is fitted. On the other side the types range from 6/36 to 6/5, but the arrangement of these slightly smaller types matches in pattern and in general appearance that of the usual set of types. The patient is shown no. 1 test type; say he reads three lines, showing vision to be 6/24. Now no. 2 test type is exposed; if he again reads three lines, his vision is really 6/18. By varying the light and by altering the size of the disks on the test card, the author believes, one can differentiate between real and feigned night blindness.

This volume is a symposium and as such portrays the individual opinions of its many authors. The articles on ophthalmic subjects contain much interesting and valuable information, and every ophthalmologist should be familiar with their contents.

JOHN H. DUNNINGTON.

Developmental Aphasia in Educationally Retarded Children. By M. MacMeekin, Ph.D., Department of Psychology, Edinburgh University. Price, 3 shillings. Pp. 95. London: University of London Press, 1942.

This monograph, another publication of the W. H. Ross Foundation for the Study of Prevention of Blindness, is partly supplemental to, and continues the investigations reported in, the author's "Ocular Dominance in Relation to Developmental Aphasia."

The "aphasic syndrome" is characterized by two major aspects: (1) word recognition difficulty and (2) strephosymbolia, or twisting of symbols. "When these characters of subnormal language achievement are found associated with left-eye dominance, a diagnosis of aphasic interference may confidently be made."

A total of 140 boys and girls (84 boys and 56 girls) included in the registry of seriously retarded children were given tests for intelligence, language attainment and laterality (eye dominance and hand dominance). The incidence of squint, latent or manifest, was noted. The intelligence tests administered were the Terman-Merrill (1937) revision of the Stanford-Binet scale. Attainment in reading was assessed on Burt's "Test of Educational Attainment." Eye dominance was determined by the cylinder test, and handedness was tested with the Van Riper apparatus.

It is not clear from the text how carefully the eyes were examined. The author refers to a previous monograph in which it is assumed to have been proved that ocular difficulties are not an important factor in reading difficulties—but the reference shows that only 36 of 383 subjects were given complete ocular tests.

The body of the monograph consists of tables and charts showing incidences and correlations between the factors under investigation. The author concludes: "The overwhelming suggestion is that this so-called developmental aphasic context is a context of sinistral tendency and sinistral expression."

As in the first monograph, little has been written concerning possible forms of therapy, probably for the reason that until a clearer idea of the etiologic foundation emerges little of rational value in this direction may be expected.

LEGRAND H. HARDY.

Ophthalmology and Otolaryngology. Military Surgical Manuals, Volume II. Edited by the Subcommittee on Ophthalmology and Otolaryngology of the Committee on Surgery of the Division of Medical Sciences of the National Research Council. Price, $4. Pp. 331, with 124 illustrations. Philadelphia: W. B. Saunders Company, 1942.

The Division of Medical Sciences of the National Research Council has furnished the medical departments of the United States Army and Navy with the information, in compact form, necessary to persons practicing military surgery. The subcommittee which covers the field of ophthalmology consists of Drs. H. S. Gradle as chairman, W. L. Benedict, S. R. Gifford, P. C. Kronfeld and L. T. Post, with W. F. Hughes Jr. and Alan C. Woods as contributors. As the committee states in the preface, the main purpose of this manual is to instruct the nonspecialist who at the battle front requires knowledge of the early care of ocular wounds and of the treatment of the usual acute inflammations of the eye. The subject matter is presented in the simplest and most practical manner in a clear, explicit and brief text, with few illustrations and with an outline of the simplest but necessary treatment.

The subject is divided as follows: Chapter I, Functional Testing, L. T. Post; II, Examination of Eye, L. T. Post; III, Acute Visual Disturbance, P. C. Kronfeld; IV, Acute Inflammations of the Eye, H. S. Gradle; V, Injuries of the Eye, S. R. Gifford; VI, Medical Treatment, P. C. Kronfeld; VII, Local Anesthesia About the Orbit, W. L. Benedict, and VIII, Surgical Procedures, W. L. Benedict. The section on chemical burns of the eye, in the chapter on injuries, is written by A. C. Woods and W. F. Hughes Jr.

The selection of authors vouchsafes an excellent presentation of a subject in which it is difficult to decide what is essential for the nonspecialist on duty with the troops to know and to do, since there are experienced ophthalmologists at the base hospitals. The chapter on injuries, which include discussion on the important subject of chemical burns, and the one on medical, or nonsurgical, treatment are especially worthy of comment and add greatly to the practical value of the volume.

ARNOLD KNAPP.

Manual práctico de oftalmología. By Raul Arganaraz. Third edition. Pp. 817, with 695 illustrations, many in colors. Buenos Aires, Argentina, El Ateneo, 1942.

The first edition of this well known textbook of ophthalmology by Dr. Arganaraz, professor at the University of Buenos Aires, was published in 1929, and since then the book has found a field of usefulness in some of the Spanish-speaking countries. The author has had more than thirty years of professional experience in teaching and clinical work in the university hospital. In his preface to this edition he asserts that as ophthalmology has had such an enormous increase, both from the clinical and from the surgical standpoint, it becomes more and more difficult for the student to obtain the basic knowledge which its progress requires. Even new and autonomous specialties, such as ocular neurology, biomicroscopy, refraction and pathologic anatomy, have grown inside the

specialty. Professor Arganaraz' book is written from the practical standpoint and contains only the basic subjects that every one must learn as a foundation for obtaining later a large and more complete knowledge in ophthalmology. For the Spanish-speaking student the book has the same field of usefulness as the May textbook of ophthalmology has for the English-speaking student. It is unfortunate that it is not known as it should be in Latin American countries other than Argentina.

This new edition is beautifully illustrated and has excellent color pictures and charts of diseases of the anterior segment of the eye and also of some of the fundus diseases. Considering that these color plates are printed in the text and not on special paper, as is usual, with a few exceptions they are excellent. Even practitioners of ophthalmology may find it interesting and profitable to read some of the chapters of the book, for instance those on perimetry and on motor disturbances of the eye. However, little attention has been given to biomicroscopy in connection with diseases of the external segment of the eye. There is practically nothing about the use of this method in the treatment of corneal disturbances. The student educated in modern schools and clinics, where he uses slit lamp microscopy almost every day, will find this a serious omission. It is to be hoped that it will be remedied in other editions of the book. The chapter on corneal grafting mentions only the work of Franceschetti and omits the operation of Castroviejo with the square corneal flap. No mention is made, even in passing, of the method of examination of the angle of the anterior chamber with the gonioscope.

The book is clearly and concisely written and will be an interesting addition to the library of any Spanish-speaking student or ophthalmologist.

MANUEL URIBE TRONCOSO.